The cyclisation of benzylaminoacetonitriles: Evidence of exclusive participation of a spirocyclic intermediate.

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THE CYCLISATION OF BENZYLAMINOACETONITRILES- Evidence of Exclusive Participation of a Spirocyclic Intermediate

submitted by

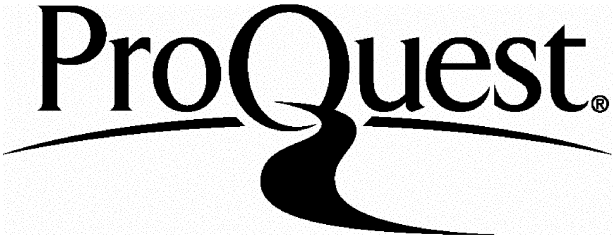
Fazal Hussain, B.Sc., M.Sc.

for the degree of Doctor of Philosophy

of the University of Bath

1985

The research has been carried out in the School of Pharmacy and Pharmacology of the University of Bath, under the supervision of Dr. D.N. Harcourt, B.Pharm., Ph.D., M.P.S. and Dr. N. Taylor, M.Sc., Ph.D., F.P.S., C.Chem., M.R.S.C.



To my parents and Azrah.

ACKNOWLEDGEMENTS

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SUMMARY

A survey has been made of isoquinoline preparation via Pomeranz-Fritsch and benzylaminoacetonitrile syntheses.

Over the past fifteen years considerable effort has been made to establish the mechanism by which cyclisations of 3,4-dialkoxybenzylaminonitriles proceeds.

Initially a dual mechanism was postulated, one mode involving an electrophilic attack *para* to the C3-substituent and the second involving attack *para* to the C4-substituent.

Recent evidence from the cyclisations of the isomeric ethoxymethoxybenzylaminoacetonitriles suggested that only the second mechanism may be operating, giving a spiro-intermediate which undergoes rearrangement to an iminium ion, followed by a Pictet-Spengler cyclisation.

However, since no attempt has been made to fully characterise the composition of the crude reaction products (dialkoxy and phenolic isoquinolinones), the classical cyclisation could not be precluded.

The work described in this thesis involves preparation and cyclisation of a series of aminonitriles at three different temperatures, -10°, room temperature and 50° followed by chromatographic analysis (t.l.c.) and separation of the crude products.

All results obtained indicate that cyclisation proceeds *exclusively* via the spiro-intermediate. No products arising from classical cyclisation were obtained.

The yield of the products obtained from all cyclisations depended upon the temperature of the reactions. For example, at -10^{o} and room temperature the major products are dialkoxyisoquinolinones, whereas at 50^{o} O-dealkylation readily occurs to give phenolic products.

Orientation of substitution was unequivocally established by means of ^{1}H n.m.r. (NaOD shift), ultra-violet spectroscopy and by preparing 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline derivatives.

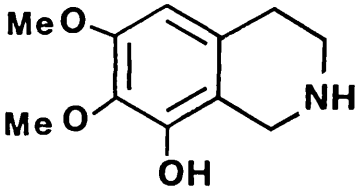
A minor part of this work involves a reinvestigation of the cyclisation of 3,4-dimethoxybenzylglycine esters to establish whether the above mechanism was involved. However, unlike the nitriles, the glycine esters failed to cyclise readily in sulphuric acid.

PART I

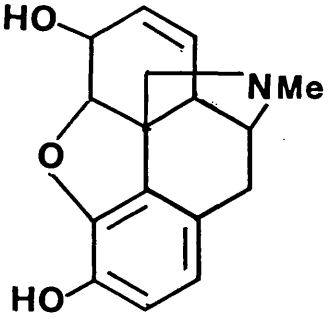
INTRODUCTION

1.1 The isoquinoline ring system

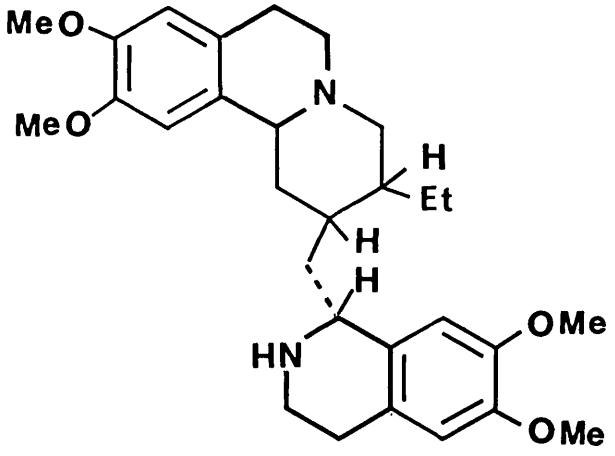
The isoquinoline ring system is widely distributed in nature[1,2] occuring in alkaloids which are simple isoquinoline derivatives (for example anhalamine) to more complex structures, such as morphine and emetine.



Anhalamine



Morphine



Emetine

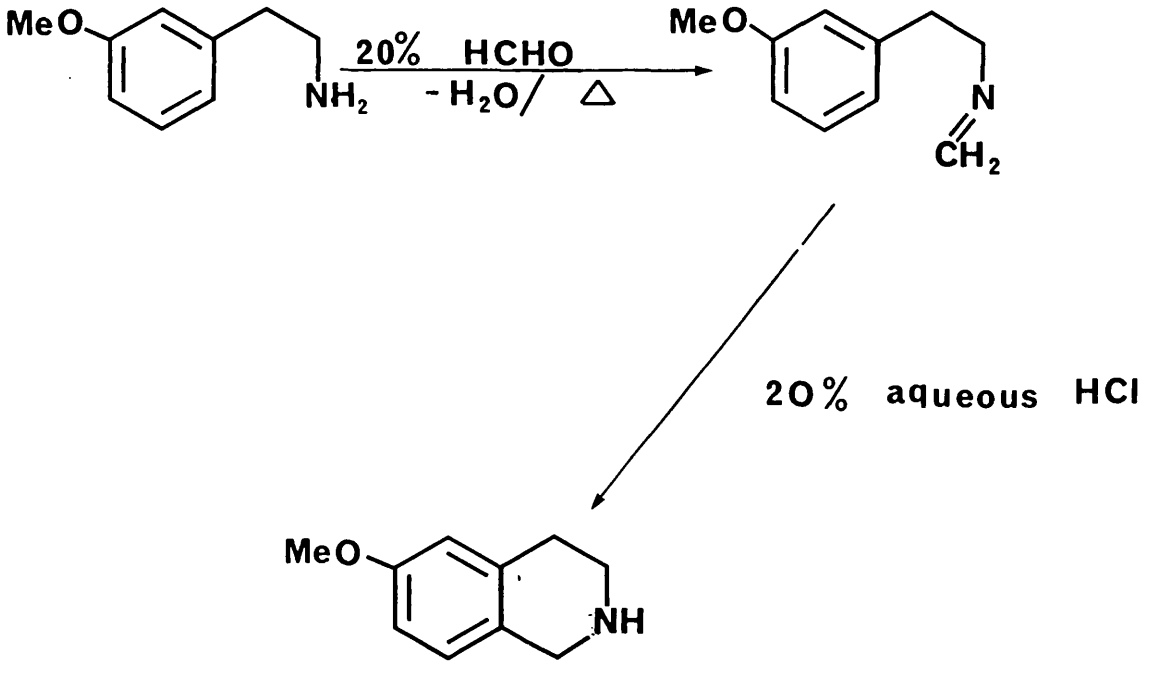
Various synthetic routes have been developed to synthesise isoquinolines. These may be divided into three main groups, namely:-

a. Cyclisation of β-phenylethylamine derivatives as in

the Bischler-Napieralski and Pictet-Spengler cyclisations together with their modifications. Both methods have been extensively reviewed[3,4].

The Pictet-Spengler Synthesis

The Pictet-Spengler Synthesis is a special case of a Mannich reaction[17] consisting of condensing of β-arylethylamine with a carbonyl compound under acidic conditions (dilute hydrochloric acid) to yield a tetrahydroisoquinoline (scheme 1).



Scheme 1

b. Cyclisation of N-(o-carbalkoxybenzyl) glycine ester exemplified by the Dieckmann condensation employed by Hinton and Mann[5] in the preparation of a

4-ketotetrahydroisoquinoline. Such a method is severely limited by the difficulty in preparing suitable intermediates.

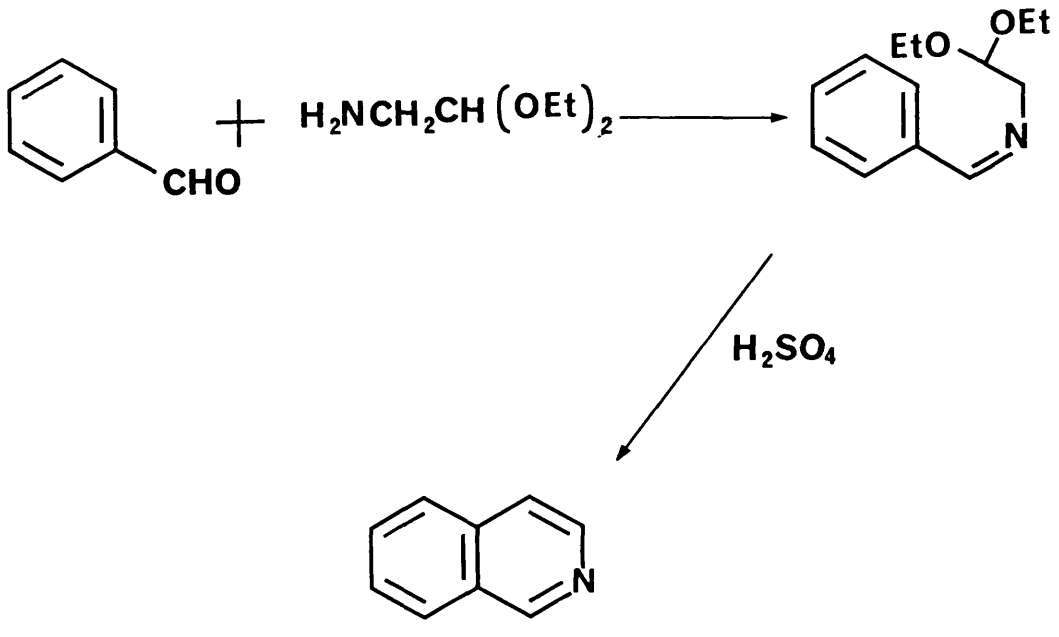
c. Cyclisation of benzalamine and benzylamine derivatives.

1.2 The Pomeranz-Fritsch Synthesis and its modifications

For many years this has been the only route to 7,8-disubstituted isoquinolines, an orientation unattainable directly by either the Bischler-Napieralski or Pictet-Spengler cyclisations. The method has been reviewed[6] and many failures reported[7] but in recent years this approach has been favoured.

1.2.1 Cyclisation of benzylideneaminoacetals

The cyclisation of benzylideneaminoacetals was first reported by Pomeranz[8-10] and by Fritsch[11,12]. The synthesis consisted of condensing an aromatic aldehyde with an amino acetal to yield a Schiff base, followed by cyclisation with sulphuric acid to yield a fully aromatic isoquinoline (scheme 2).

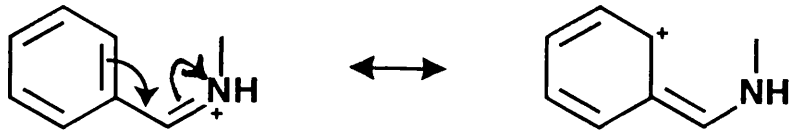


Scheme 2

The yield of isoquinoline obtained appears to be critically linked to the concentration of the sulphuric acid. If the concentration is too low, hydrolysis of the benzylaminoacetal to its components occurs, whereas extensive decomposition results when the concentration of acid is too high.

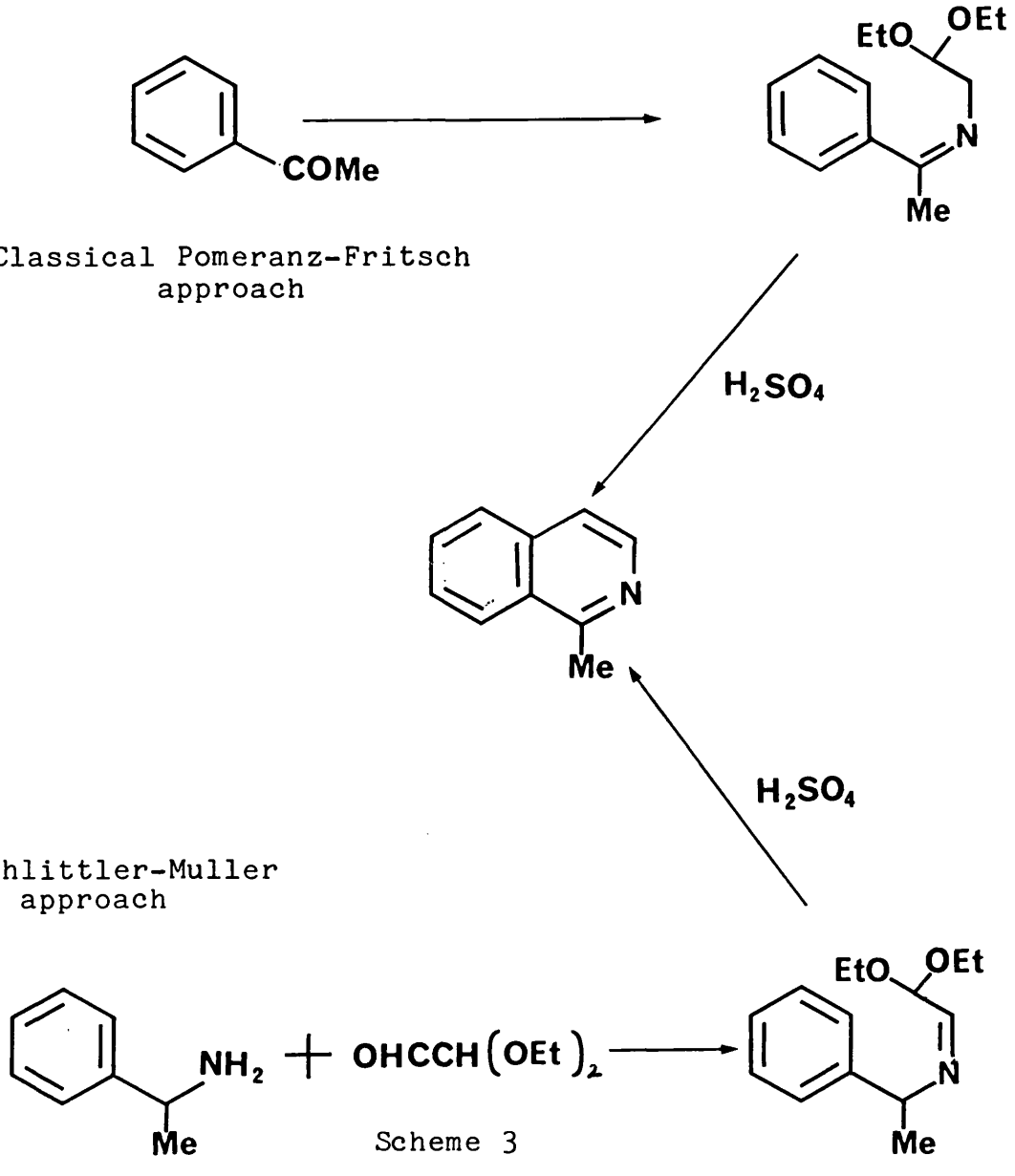
The use of strong acid in the course of ring closure suggests the operation of an electrophilic process. Therefore the ease of cyclisation would depend on the presence of electron donating groups in the aromatic ring, this feature is lacking in the original Pomeranz-Fritsch reaction.

Another factor which tends to affect the yield of the product is the deactivation of the aromatic ring. This, in the cyclisation under the above conditions, is the result of the electron with drawing effect of the protonated imino group, which inhibits electrophilic substitution of the ring.



These problems led to the development of alternative cyclising agents. For example polyphosphoric acid - phosphorus oxychloride[13], polyphosphoric acid[14] and borontrifluoride - trifluoracetic anhydride[15]. Some improvements have been achieved but many yields are still poor.

Furthermore, poor results are usually obtained when aromatic ketones are substituted for aldehydes, possibly due to difficulty in the condensation of the ketones with aminoacetals to yield the Schiff bases. These disadvantages were partially overcome by Schlittler and Muller[16]. For example, α-phenylethyl amine was first converted to the Schiff base with glyoxal semiacetal. On treatment with concentrated sulphuric acid at 160°, 1-methylisoquinoline was isolated in 40% yield as compared with the route involving reaction between acetophenone and the aminoacetal, which gave a 5% yield only (scheme 3).



Scheme 3

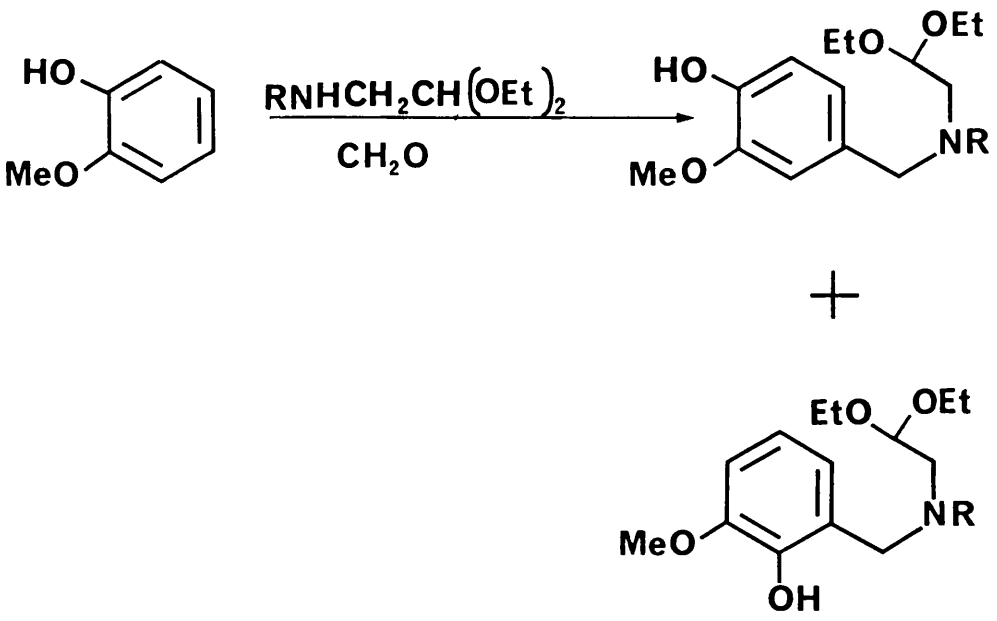
1.2.2 Benzylaminoacetals

a. Synthesis of benzylaminoacetals

The preparation of benzylaminoacetals has been reviewed by Bobbitt and has been achieved by three main routes.

i. Via the Mannich reaction[17].

This approach involves the condensation of phenols with formaldehyde and an aminoacetal to give the required starting material[18,19]. The major disadvantage of this route is that the Mannich condensation can take place ortho or para to the phenolic hydroxyl group, therefore, resulting in a mixture of isomers. This is well illustrated for example, by guaiacol which yields both the 4-hydroxy-3-methoxy-benzylaminoacetal and the 2-hydroxy-3-methoxy isomer (scheme 4).

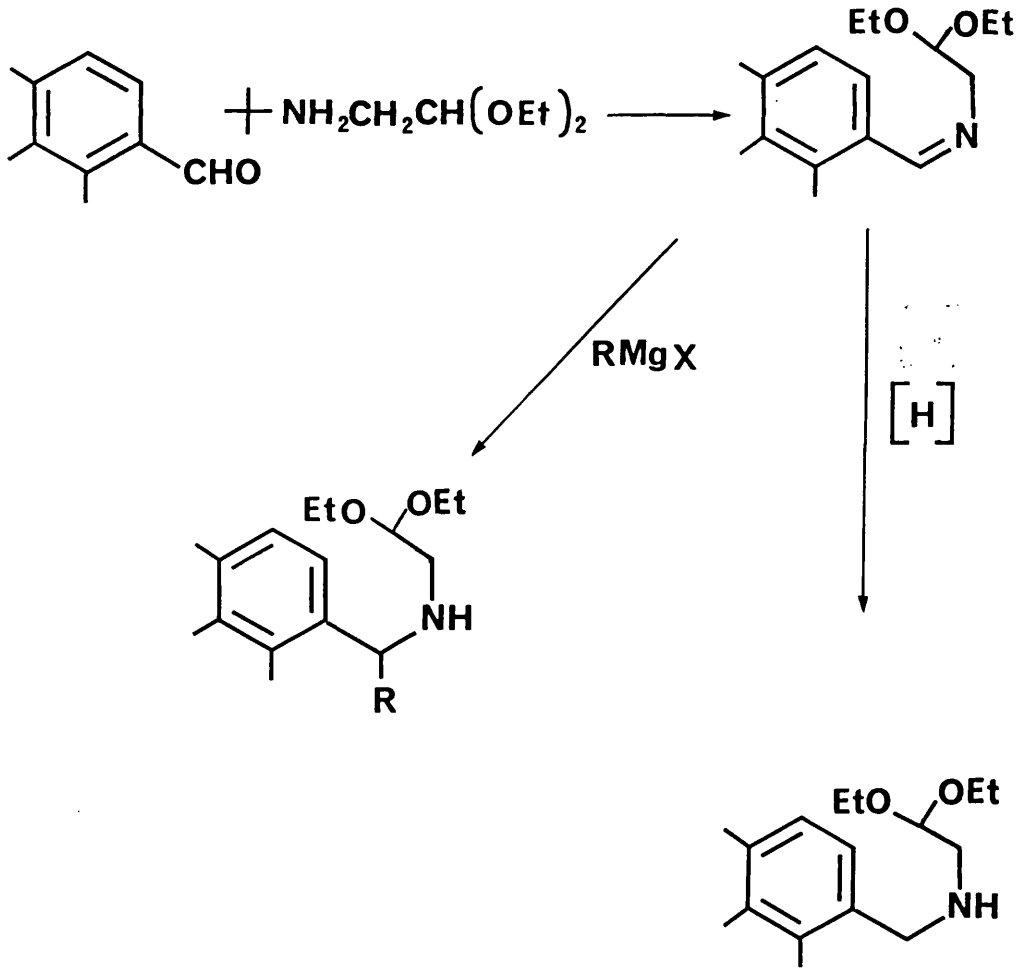


Scheme 4

ii. From aromatic aldehydes.

The Schiff bases which are used in the original Pomeranz-Fritsch Synthesis can either be reduced by catalytic methods[20,21] or by sodium borohydride[22] to yield benzylaminoacetals. Im most cases, the reduction is achieved directly without isolation of the Schiff base.

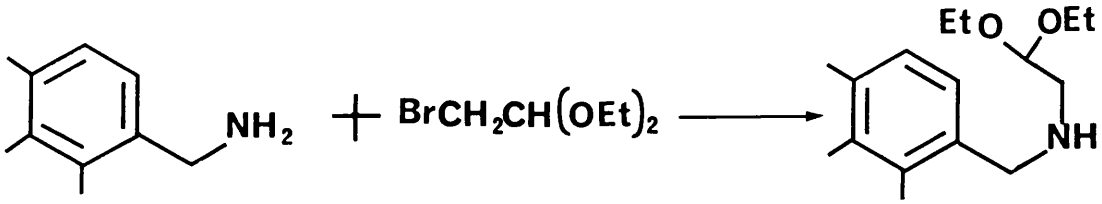
Several groups of workers[21,23-25] have used the reaction of a Grignard reagent with the imine to effect reduction of the imino function and introduction of a substituent at the benzylic position (scheme 5).



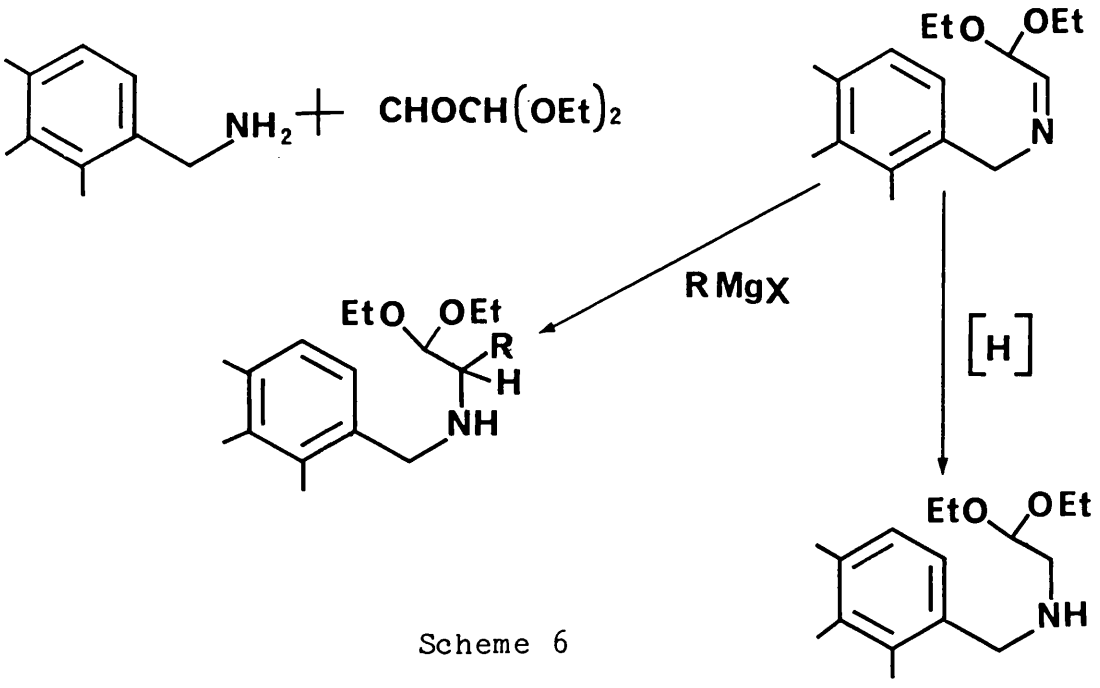
Scheme 5

iii. From Benzylamines.

Benzylaminoacetals have been prepared from benzylamines by essentially three routes. The oldest of these was first used by Young and Robinson[26] and involves reaction between excess of the benzylamine and bromoacetaldehyde diethyl acetal.

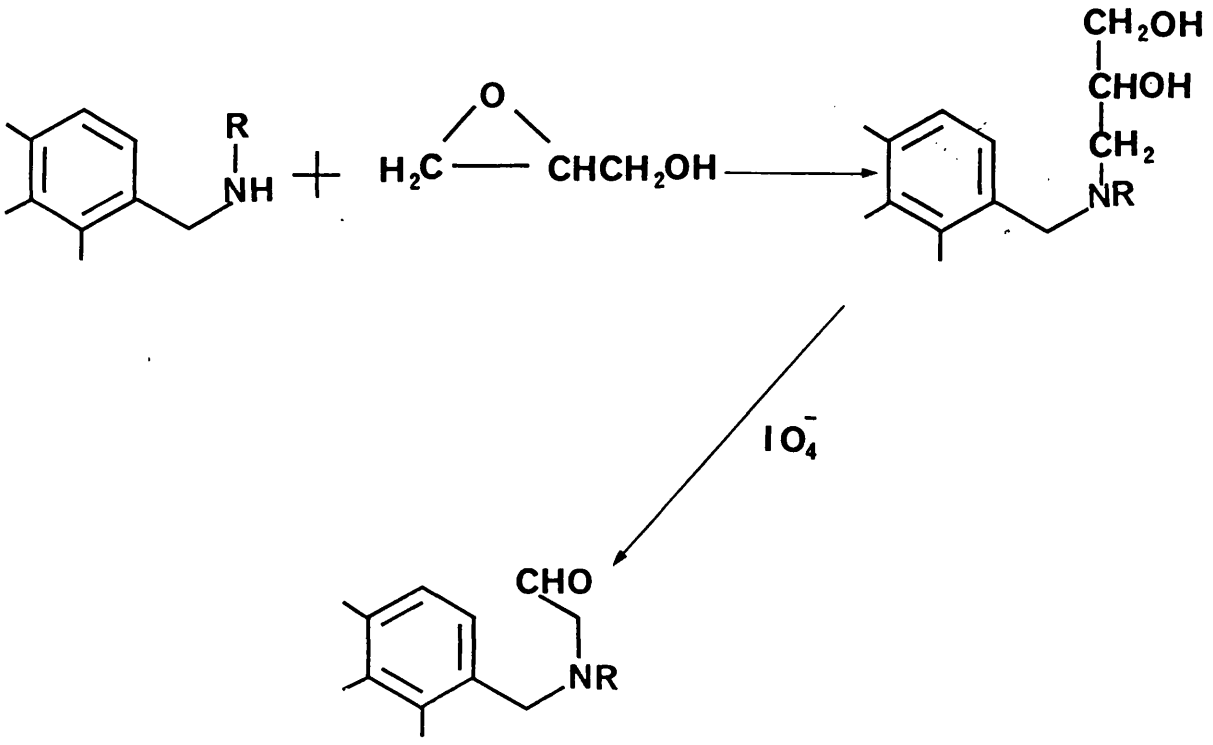


The second route involves the condensation of a benzylamine with glyoxal semiacetal. This approach was devised by Schlittler and Muller[16] (scheme 6) and offers a method of preparing 3-substituted tetrahydroisoquinolines.



Scheme 6

The third method which was developed by Frank and Purves[27] and later by Bobbitt and co-workers[33] is most suitable for preparing the N-alkyl tetrahydroisoquinolines (scheme 7). The procedure involved reaction between the secondary benzylamine and glycidol to yield an amino glycol which upon cleavage with periodate gave the benzylamino-acetaldehyde.

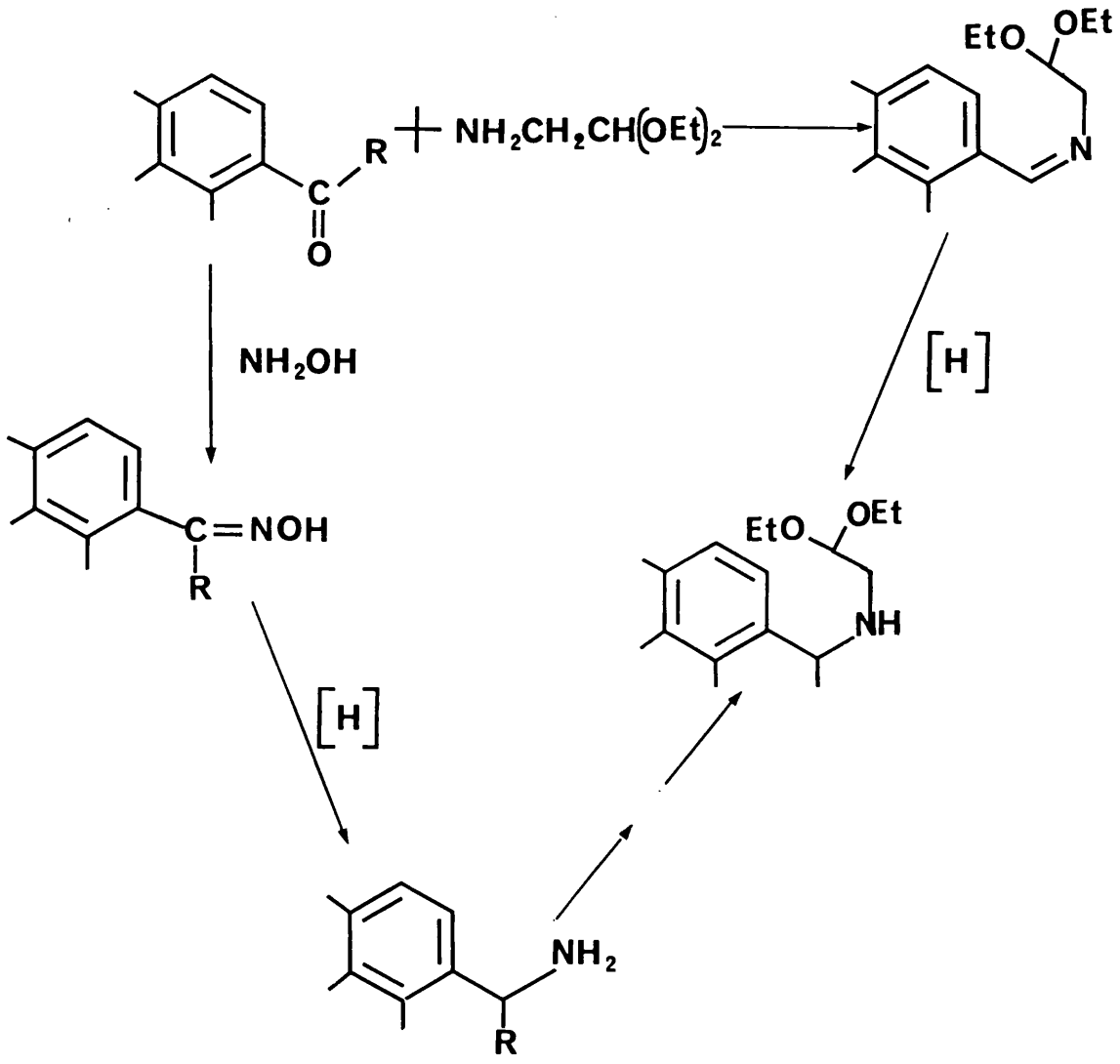


Scheme 7

iv. From ketones.

The synthesis of benzylaminoacetals from ketones and aminoacetals is identical to the procedure used for aldehydes, but experimentally the condensation between ketone and aminoacetal is more difficult. This is presumably due to the low order of reactivity of the ketones with primary amines.

However, in the case of simple acetophenones the difficulties have been overcome by carrying the reaction in absolute alcohol[22]. In other cases[28,29] the benzylamino-acetals were prepared by heating the reactants without a solvent at 105-125° under nitrogen followed by the catalytic reduction over platinum (scheme 8). Perhaps the better procedure is to convert the ketone to a substituted benzylamine and then proceed via the Schlittler and Muller[16] route (as in iii).

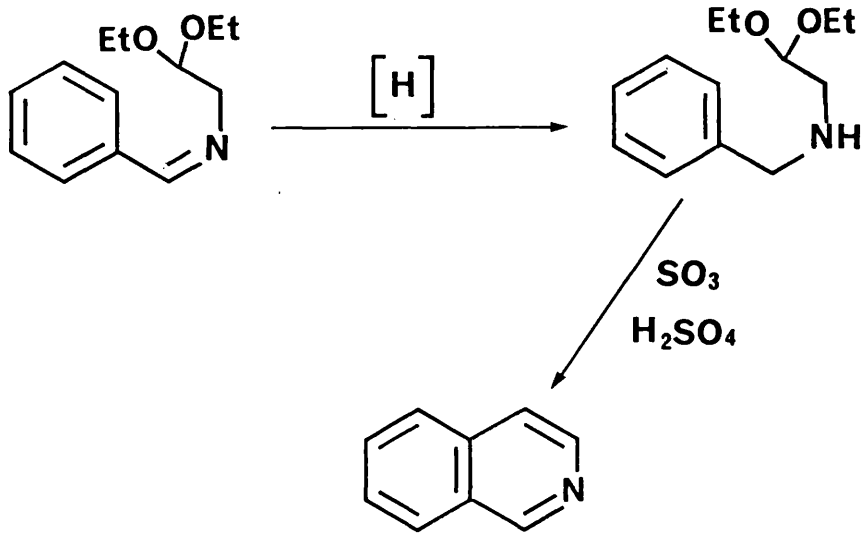


Scheme 8

b. **Cyclisation of benzylaminoacetals.**

Various modifications have been made with respect to the type of acidic reagent used to effect the ring closure of benzylaminoacetals.

Cyclisation of benzylaminoacetals were first reported by Fischer[30]. He used fuming sulphuric acid which not only served as cyclising agent but also as an oxidizing agent to yield the fully aromatic product (scheme 9). Other workers[31,32] used arsenic pentoxide as an oxidizing agent, but the yields were poor.

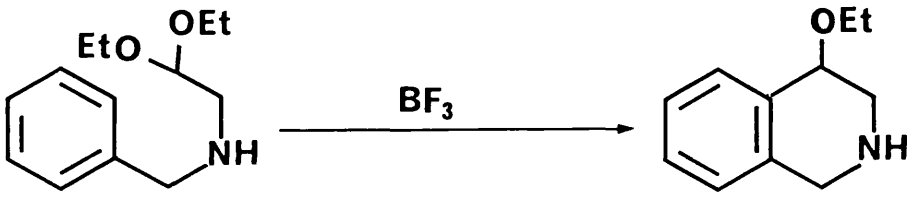


Scheme 9

The above work has been summerised by Frank and Purves[27], who with limited success attempted to prepare benzylamino-acetaldehydes and then cyclise them. This benzylamino-acetaldehyde approach was later developed by Bobbitt and co-workers[33] to prepare N-substituted tetrahydroisoquinolines.

For example, the overall yields from 3,4-dimethylene-dioxybenzaldehyde to the N-substituted tetrahydroisoquinoline were 35-65%.

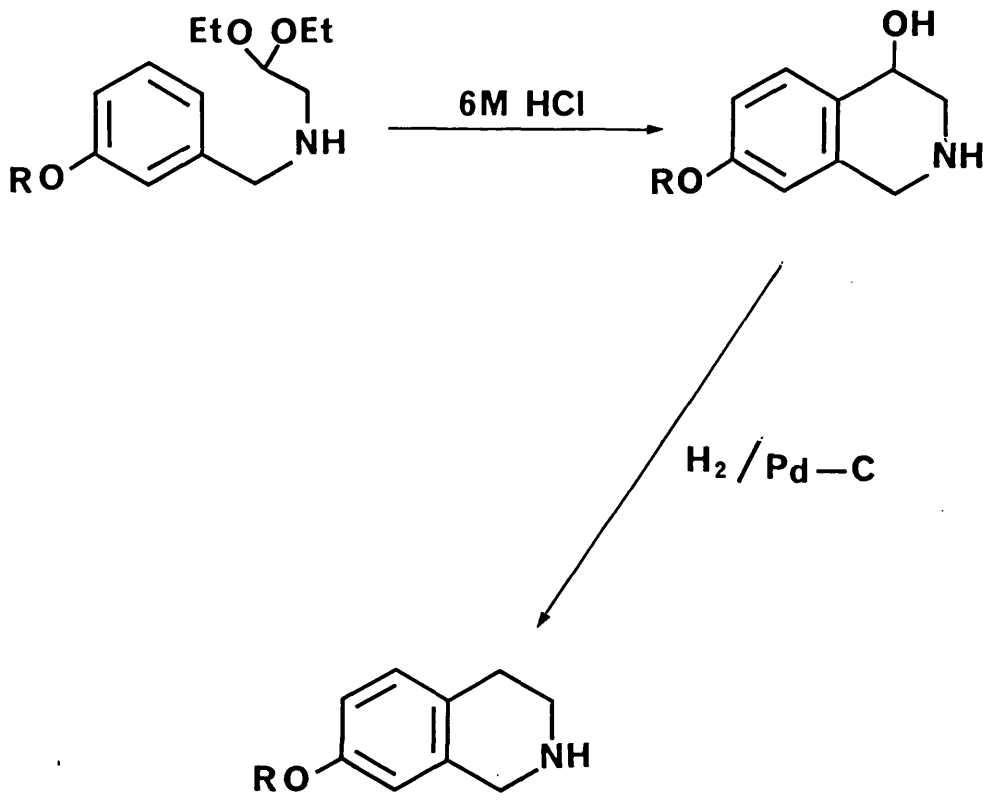
The difficulties associated with the cyclisation of the benzylaminoacetals were first overcome by Quelet and Vinot[34,35], who successfully employed boron trifluoride as the cyclising agent and the 4-ethoxytetrahydroisoquinoline was obtained.



However, the presence of an oxygenated substituent in the aromatic ring led to low yields. This is presumably due to co-ordination of the boron trifluoride with the oxygen atom causing a withdrawal of electrons from the carbocyclic ring.

Conversely Bobbitt and co-workers[36,37,38] successfully employed 6M hydrochloric acid as the cyclising agent providing an oxygenated substituent was present to activate the carbocyclic ring.

The procedure involves treatment of the benzylamino-acetal with 6M hydroxhloric acid for 14-18 hours at room temperature. Removal of acid under reduced pressure gave good yields of the 4-hydroxytetrahydroisoquinoline hydro-chloride, which upon hydrogenolysis was converted to the tetrahydroisoquinoline (scheme 10).

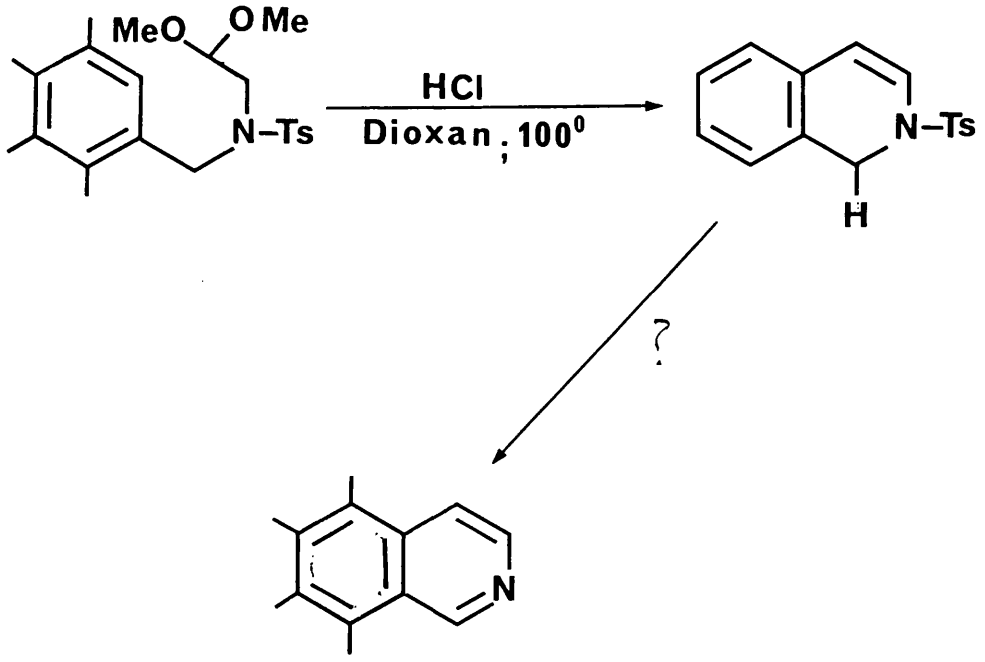


Scheme 10

Further modification of the Pomeranz-Fritsch synthesis was developed by Jackson and co-workers[39-41], who suggested that tosylation of the benzylaminoacetal, prior to cyclisation using 6M hydrochloric acid in boiling dioxan afforded improved yields of the isoquinoline.

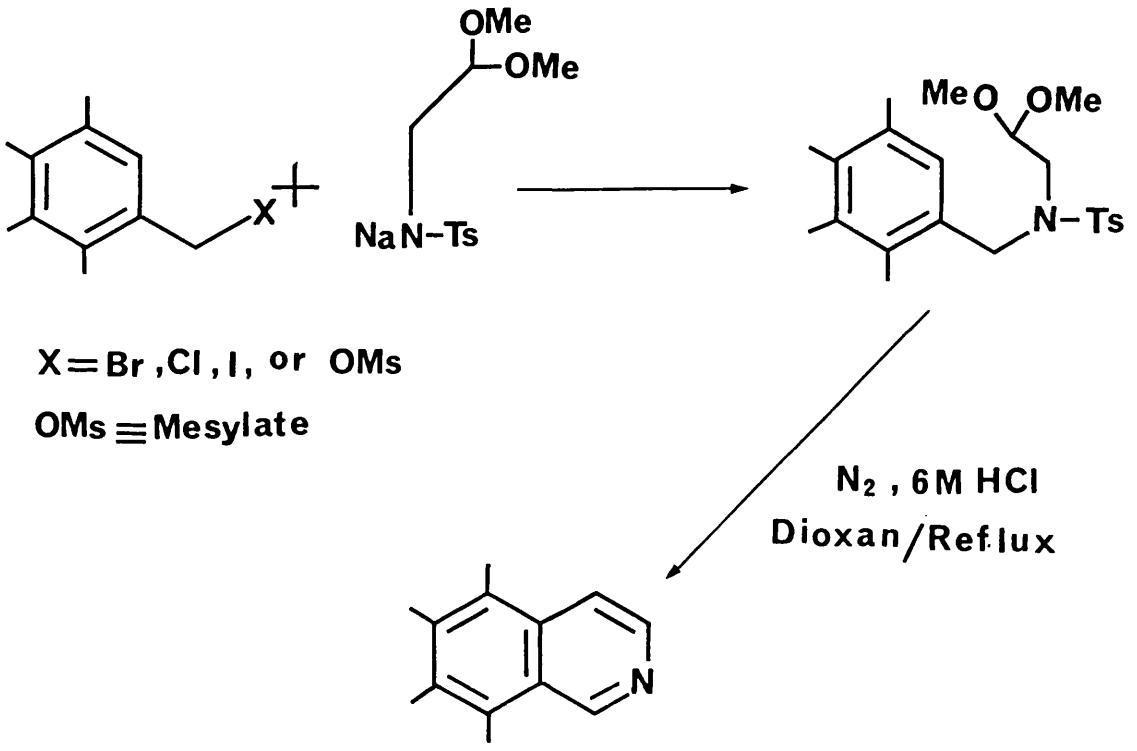
Although in most cases isoquinolines are produced directly, in some reactions detosylation was inhibited by the presence of alkoxy substituents at C6 and C8 which would donate electrons towards the benzylic group.

However, in these instances the 1,2-dihydro-N-tosyl-isoquinoline is isolated and detosylation was then achieved by using potassium t-butoxide in t-butyl alcohol (scheme 11).



Scheme 11

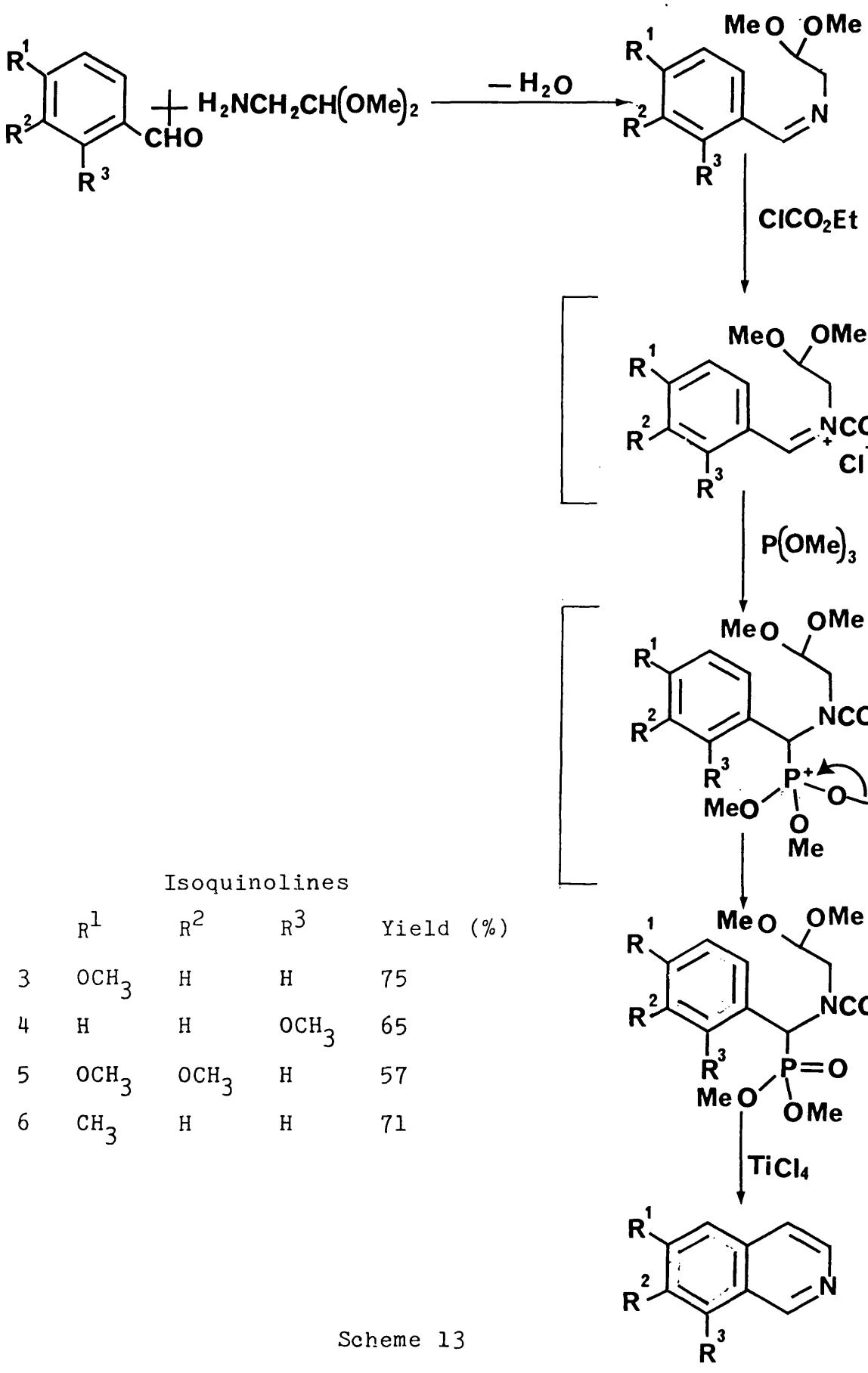
In the process of improving the original Pomeranz-Fritsch synthesis of isoquinolines (two steps, low yields), the modified sequence by Jackson and co-workers now involves four steps. This prompted Boger and co-workers[42] to develop a more convenient route to the N-tosylbenzylaminoacetal. This was achieved in one step by reaction of a benzylic halide or mesylate with the sodium salt of the N-tosyl-aminoacetal (scheme 12).



Scheme 12

More recently Hendrickson and Rodriguez[43] have offered a 'one pot' synthesis of isoquinolines (scheme 13). They suggested that the imine (1) reacts readily with ethyl chloroformate followed by trimethyl phosphite to form the intermediate carbonate phosphonate (2), which is presumably created by addition of phosphite to the acyl-activated imine. Treatment of this intermediate with titanium tetrachloride in refluxing chloroform effects cyclisation to the isoquinoline with loss of the phosphonate and carbonate groups.

It is interesting to notice that the yields in cases of the isoquinolines 3,4 and 6 in which the aromatic ring does not possess a <u>para</u> activating group are unusually good for this kind of cyclisation (scheme 13).



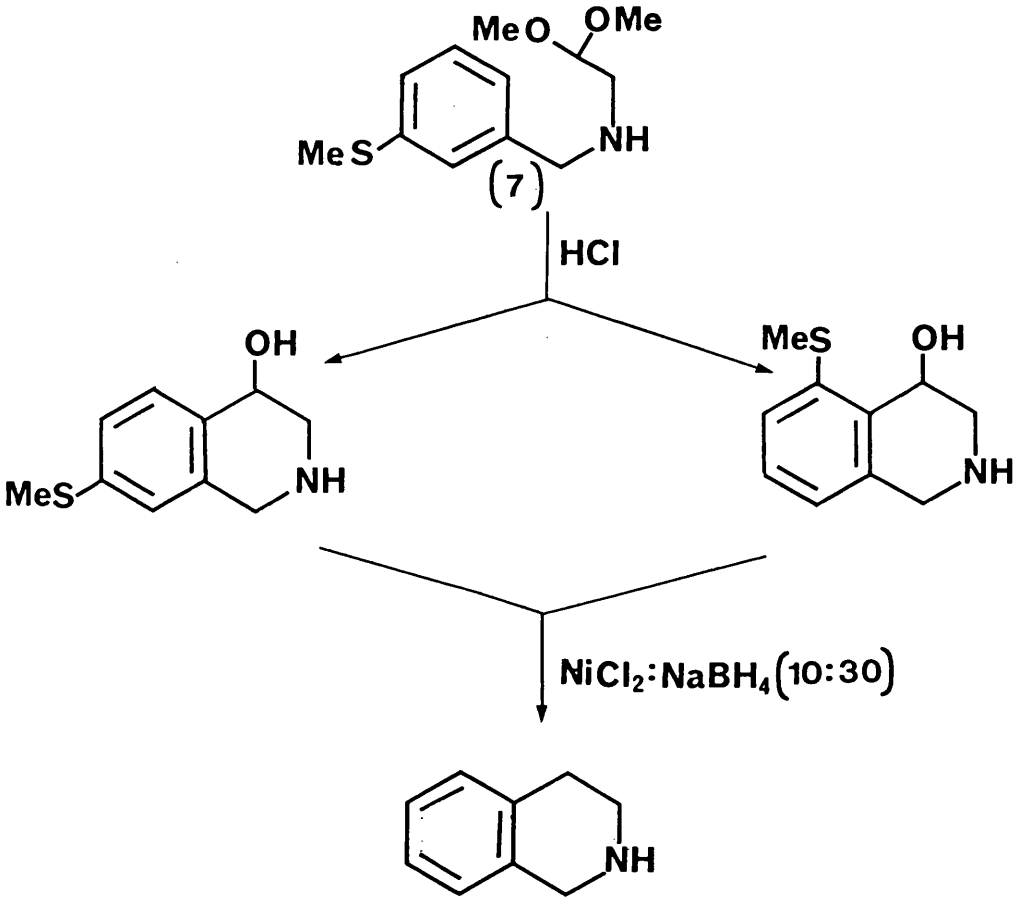
Isoquinolines

	R^1	R^2	R^3	Yield (%)
3	OCH_3	H	H	75
4	H	H	OCH_3	65
5	OCH_3	OCH_3	H	57
6	CH_3	H	H	71

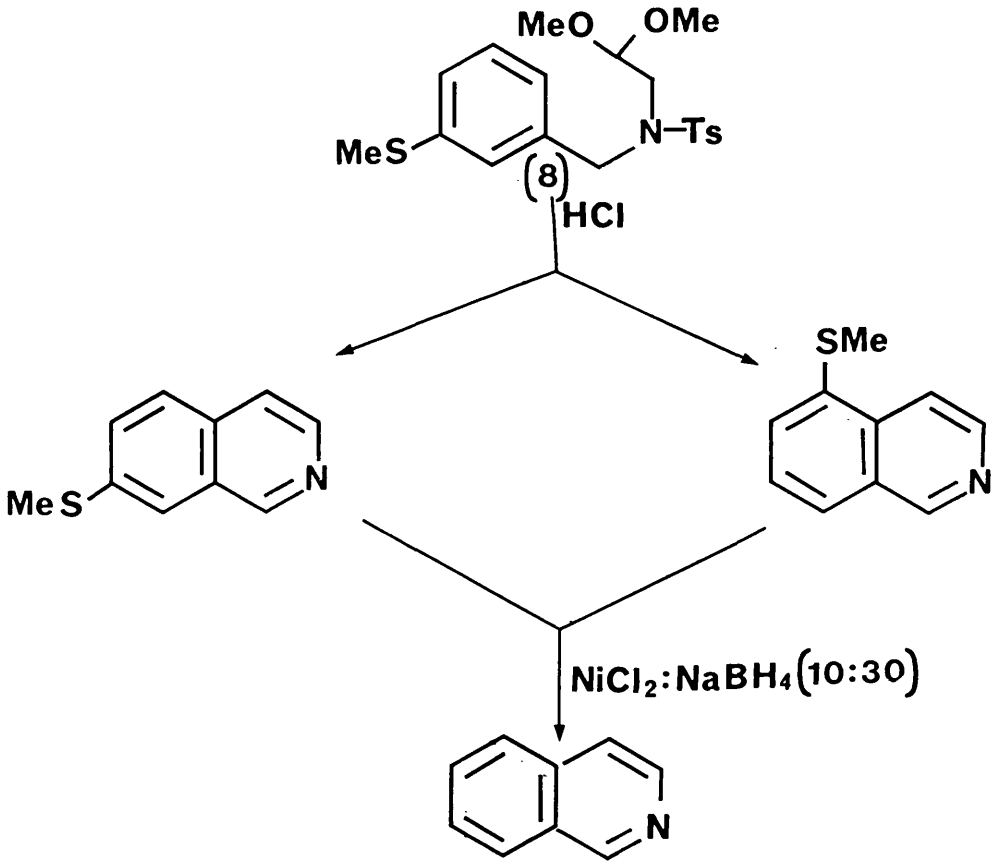
Scheme 13

Most cyclisations of the type mentioned above require activation of the carbocylic ring by an alkoxy group (such as methoxy). Such an activating group is difficult to remove after cyclisation should an unsubstituted ring be desired in the final product.

However, this disadvantage has been overcome by Euerby and Waigh[44], who used the methylthio group as an activating group, which after cyclisation was removed by reductive desulphurisation. These authors have reported that cyclisation of benzylaminoacetal (7) and its tosyl derivative (8) proceeds ortho aswell as para to an activating substituent (scheme 14 and 15).



Scheme 14



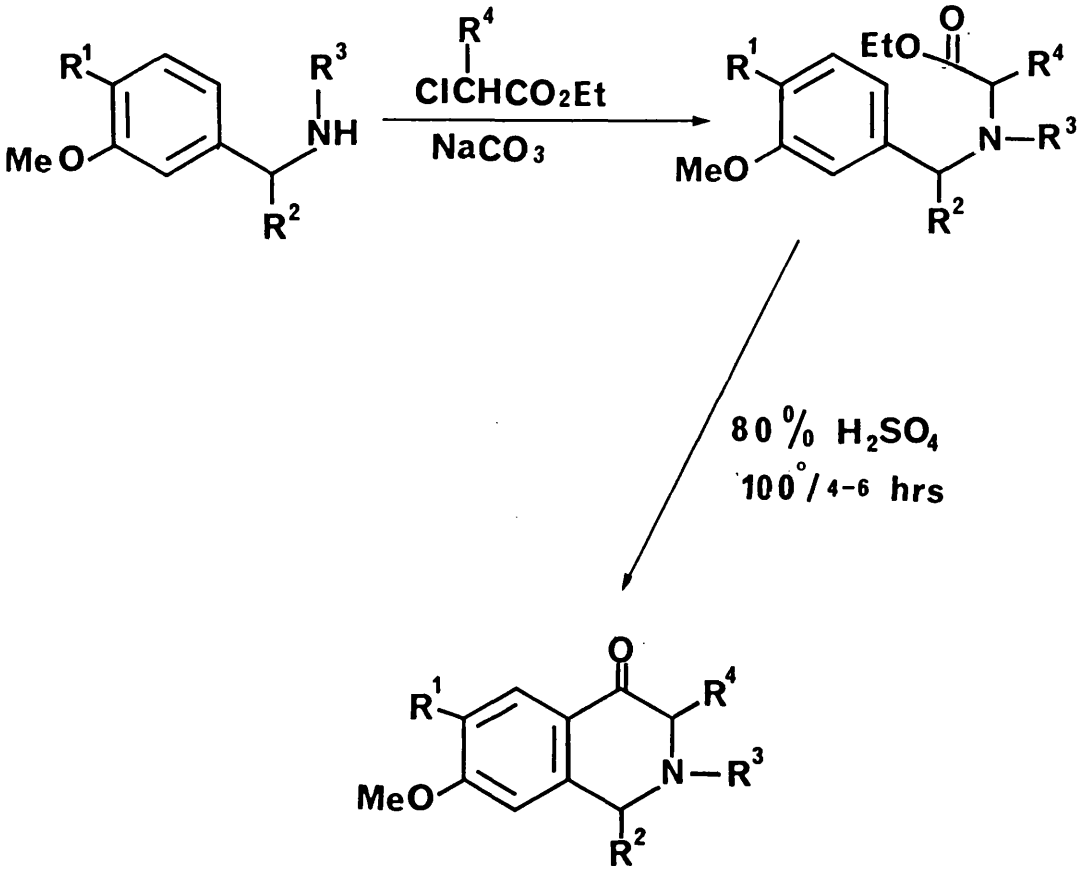
Scheme 15

Euerby and Waigh have also applied this approach to the Pictet-Spengler and Bischler-Napieralski cyclisation, in these instances no product of ortho cyclisation was reported. These authors have claimed that superior yields of the products are obtained as compared to the methoxy analogues.

1.3 Cyclisation of benzylglycine esters.

Kametani and Fukumoto[45] successfully cyclised N-(3,4-dimethoxy-α-methylbenzyl) glycine with polyphosphoric acid to 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin--4(1H)-one, the yield was poor although some improvement was achieved when amino group was protected by N-formylation[46,47].

The reaction was extended by Grethe and co-workers[48] cyclising a series of N-benzylglycine esters with 80% sulphuric acid at 100°. Moderate yields of isoquinolinones were obtained (scheme 16), especially when the benzylic carbon carried an alkyl or aryl substituent.



Scheme 16

A main disadvantage of this route is that yields are extremely low when secondary amines (R^3=H) are used or when 3,4-dimethoxybenzylglycine esters (R^1=OMe) are cyclised. For example, the cyclisation of N-benzyl derivatives of 3,4-dimethoxybenzylglycine ester gave only 10% of the N-benzyl-6,7-dimethoxyisoquinolinone.

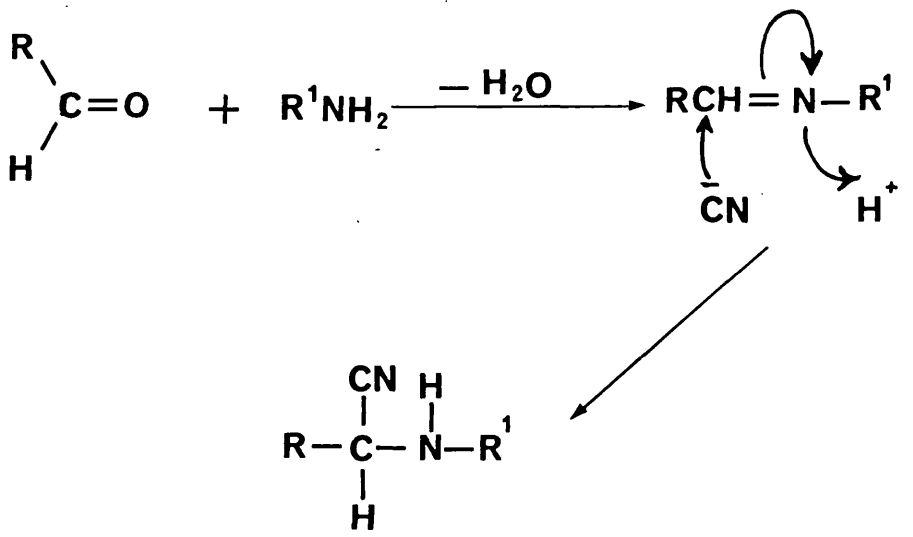
The isolation of the 6,7-dimethoxyisoquinolinone in low yield is presumably due to the extreme temperature used for the cyclisation. This possibly led to the cleavage of one or even both methoxyl groups during the course of cyclisation and thereby resulting in the phenolic isoquinolinone, which was not isolated by these authors. These disappointing results (with respect to the yield of dimethoxyisoquinolinone) prompted Grethe and co-workers to revert to using the Dieckman approach[118].

1.4 Cyclisation of Benzylaminoacetonitriles

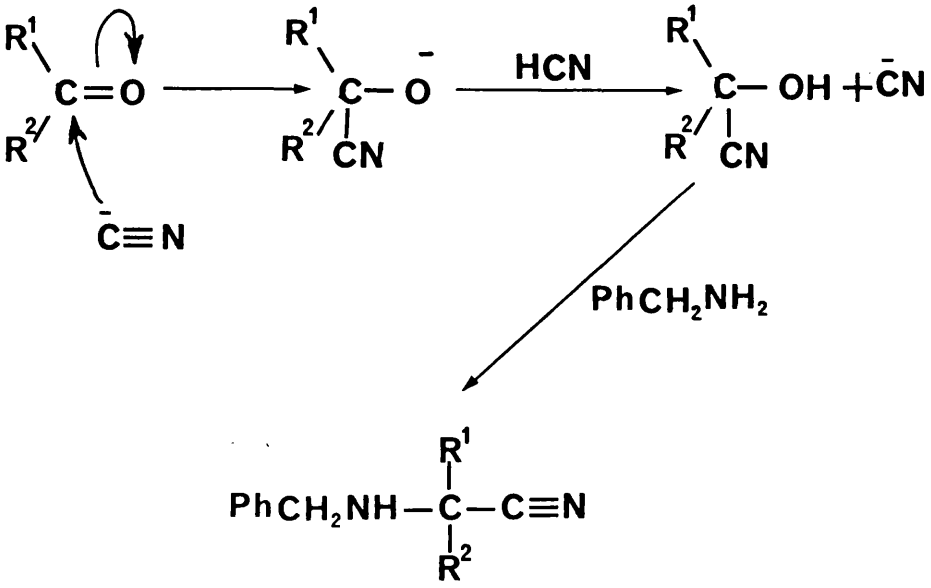
Aminonitriles

The Strecker synthesis[49] is a well-known classical procedure including its modification for the preparation of aminonitriles[50,51] from aldehydes and ketones. In general, the procedure involves reaction of equimolecular proportions of an amine salt and aldehyde or ketone with alkali cyanide in aqueous or alcoholic solution. The mechanism for the Strecker Synthesis has not been fully explained.

However, three possible mechanisms have been postulated. Firstly the reaction may proceed, particularly in the case of primary amines and aldehydes via a formation of a Schiff base followed by nucleophilic attack by cyanide ion.

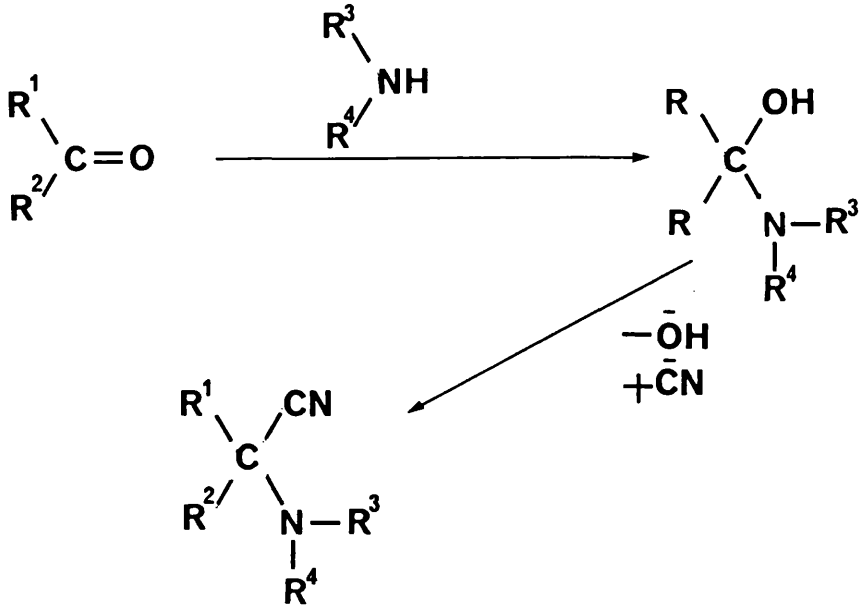


Alternatively, the nucleophilic addition of cyanide ion to the carbonyl group leads to the formation of a cyanohydrin followed by subsequent nucleophilic displacement of the hydroxyl group by the amine.



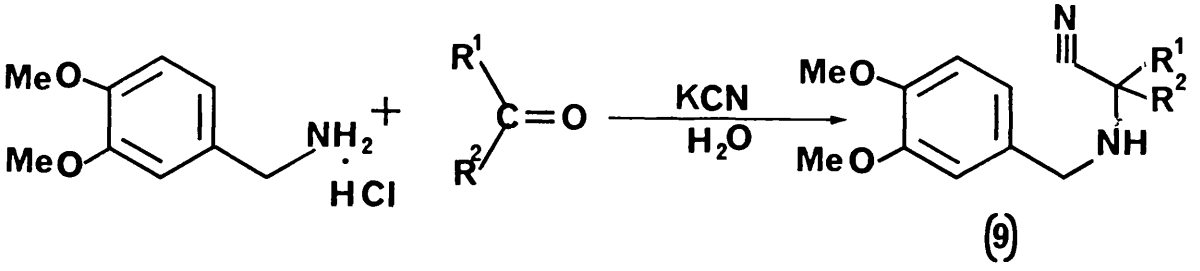
Stewart and Li[52] disputed this mechanism and supported their view with the study of rate constants for the reaction of acetone cyanohydrin with diethylamine inasolution of acetone and alcohol.

Another possibility is the formation of an aminoalcohol intermediate, which could undergo nucleophilic attack by a cyanide ion.



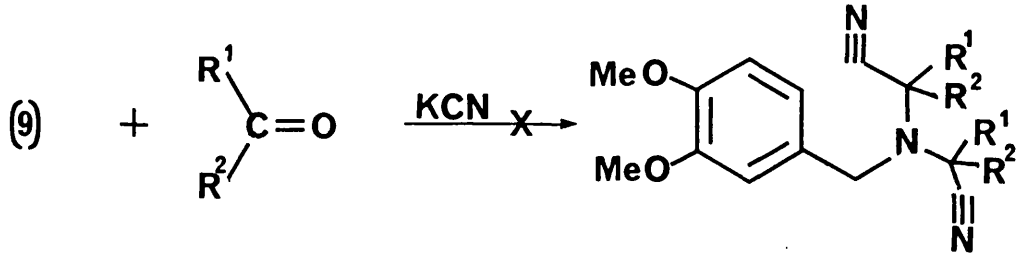
It is possible that formation of aminonitrile may well be due to a combination of all three mechamisms.

Harcourt and Waigh[51] prepared a series of benzylamino-acetonitriles (9) in excellent yields by reaction of 3,4-dimethoxybenzylamine hydrochloride, a carbonyl compound and excess potassium cyanide in aqueous or aqueous alcoholic solution.



(9)

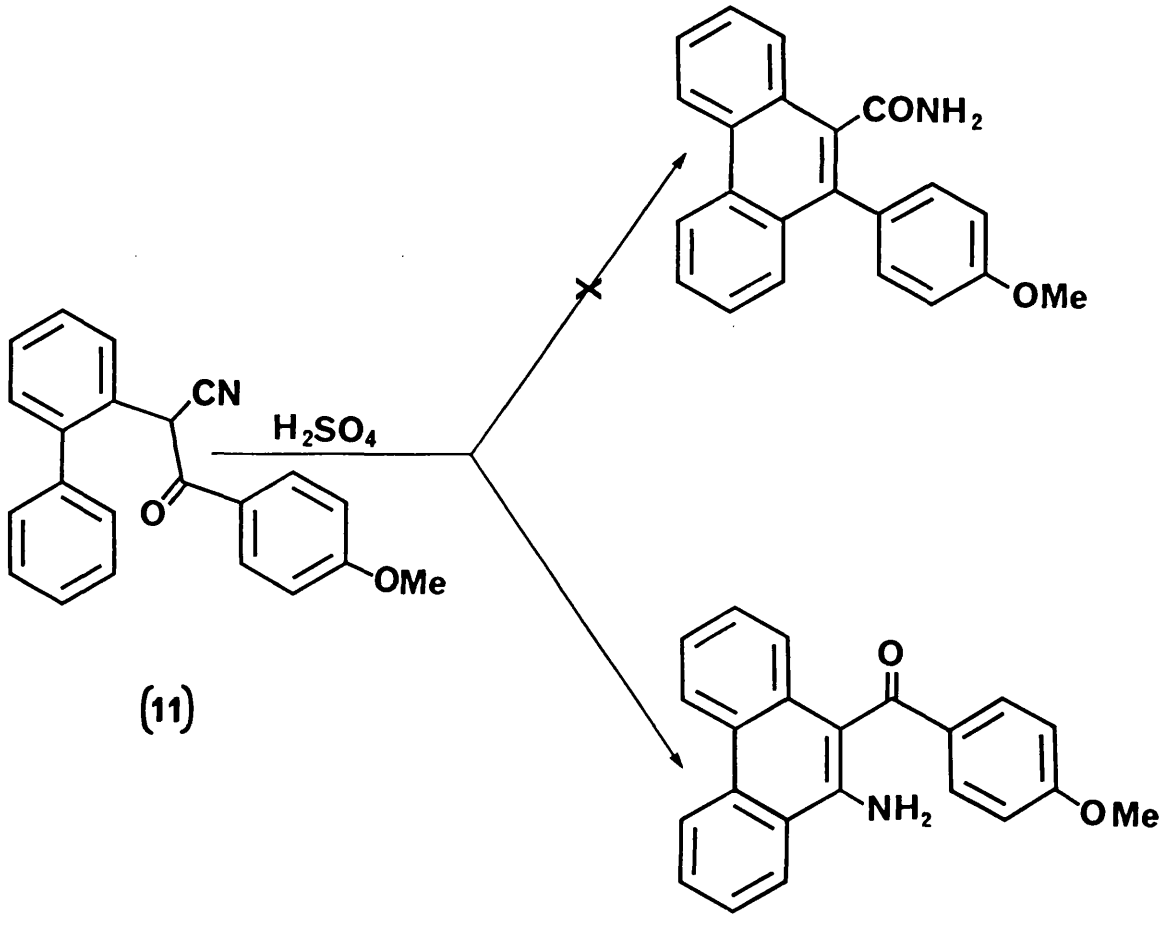
The attraction of the nitrile route is enhanced by the flexibility that the Strecker reaction permits with regard to substitution at the 3-position of the potential isoquinoline ring. Aldehydes and ketones react readily and use of excess carbonyl compound does not lead to production of the tertiary amine (10)[53] contrary to the observations of Dimroth and Aurich.



(10)

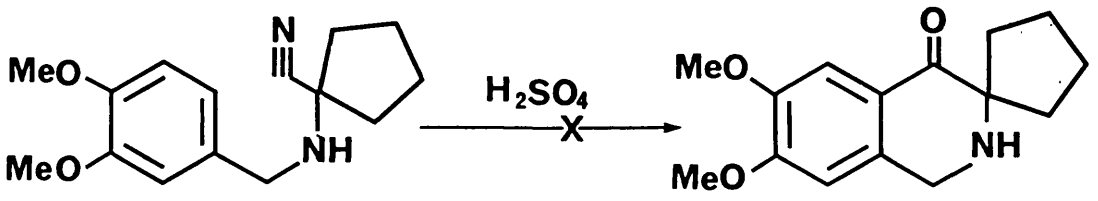
There are a number of reports in the literature of unsuccessful attempts to cyclise benzylaminonitriles. The failure by workers[54,55] who employed the use of dry hydrogen chloride under typical conditions of the Hoesch reaction[56], may be attributed to precipitation of the base hydrochloride from the reaction mixture.

However, Bradsher[57] reported a successful cyclisation of a nitrile (11) using concentrated sulphuric acid. His work was of interest in that the alternative cyclisation involving a readily enolisable ketone did not occur (scheme 17).

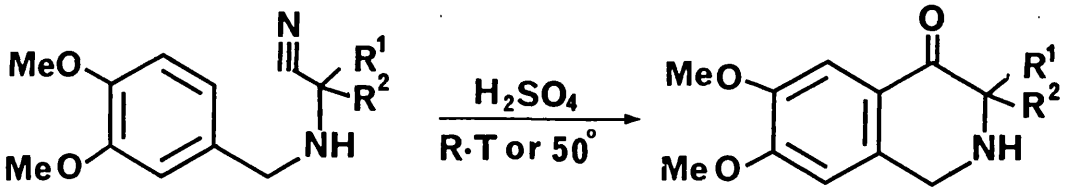


Scheme 17

The failure of Oakeshott and Plant[58], who used concentrated sulphuric acid as the cyclising agent, is difficult to explain.



Despite these failures, Harcourt and Waigh[51] found that cyclisation of 3,4-dimethoxybenzylaminoacetonitriles proceeded smoothly in concentrated sulphuric acid at 50° or room temperature, to yield the 6,7-dimethoxy-2,3-dihydro-isoquinolin-4(1H)-ones in good yield (scheme 18).

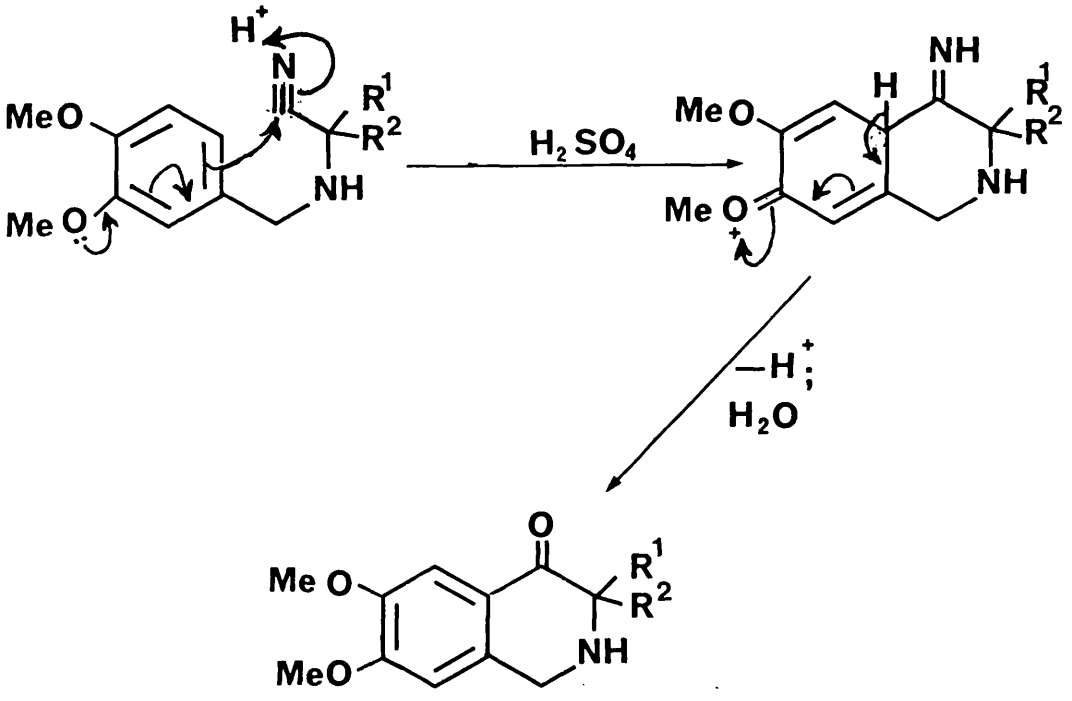


R^1	R^2	Yield (%)[51]
Ph	H	53
Ph	Me	83
Me	Me	60
$-CH_2[CH_2]_3CH_2-$		80

Scheme 18

1.4.1 Mechanism of cyclisation of Benzylaminoacetonitriles

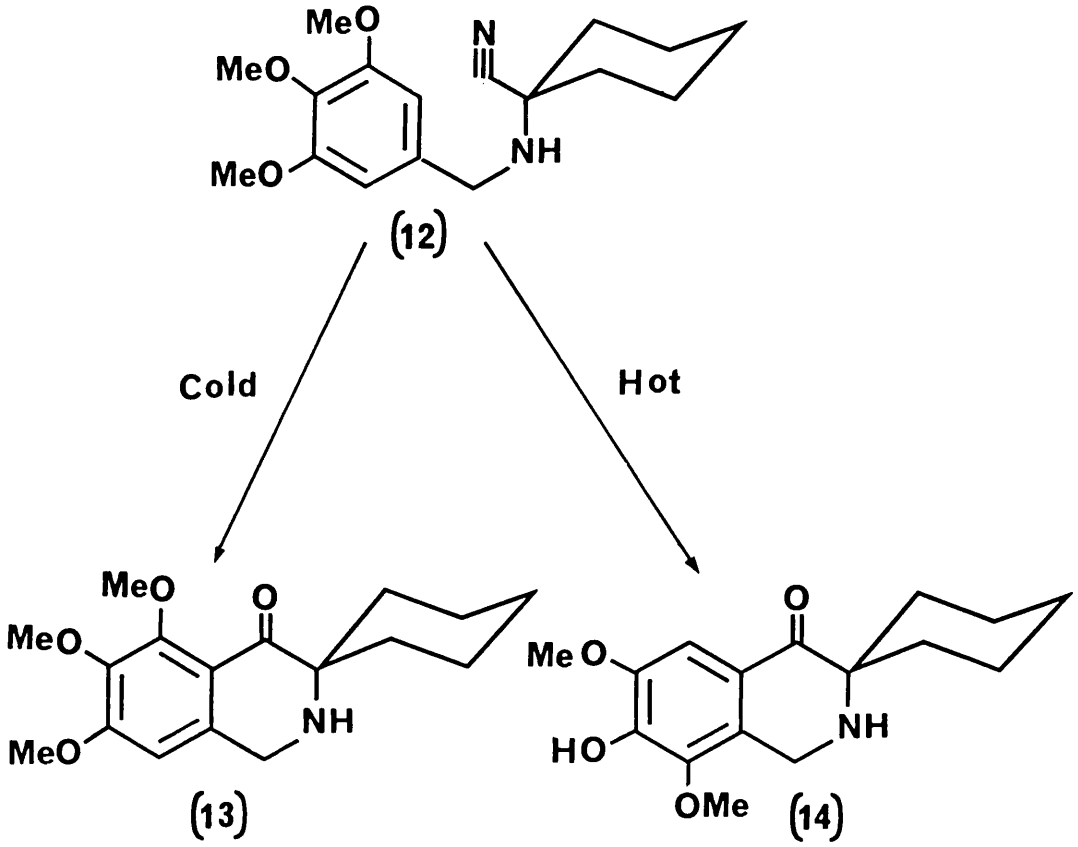
Harcourt and Waigh[51] initially assumed that cyclisation prodeeded via a classical mechanism, involving electrophilic attack para to the C3-methoxyl group (scheme 19).



Scheme 19

Subsequently[59] cyclisation of a 1-(3,4,5-trimethoxy-benzylamino) cyclohexane carbonitrile (12) at room temperature gave 3,4-dihydro-5,6,7-trimethoxyisoquinolin-3-spirocyclo-hexane-4(1H)-one (13) whereas cyclisation at 50° furnished 3,4-dihydro-7-hydroxy-6,8-dimethoxyisoquinoline-3-spiro-cyclohexane-4(1H)-one (14) (scheme 20).

To explain this Harcourt, Taylor and Waigh suggested the operation of a dual mechanism, one involving a classical ortho cyclisation as shown in scheme 19 and the other involving electrophilic attack para to the C4-methoxyl group.



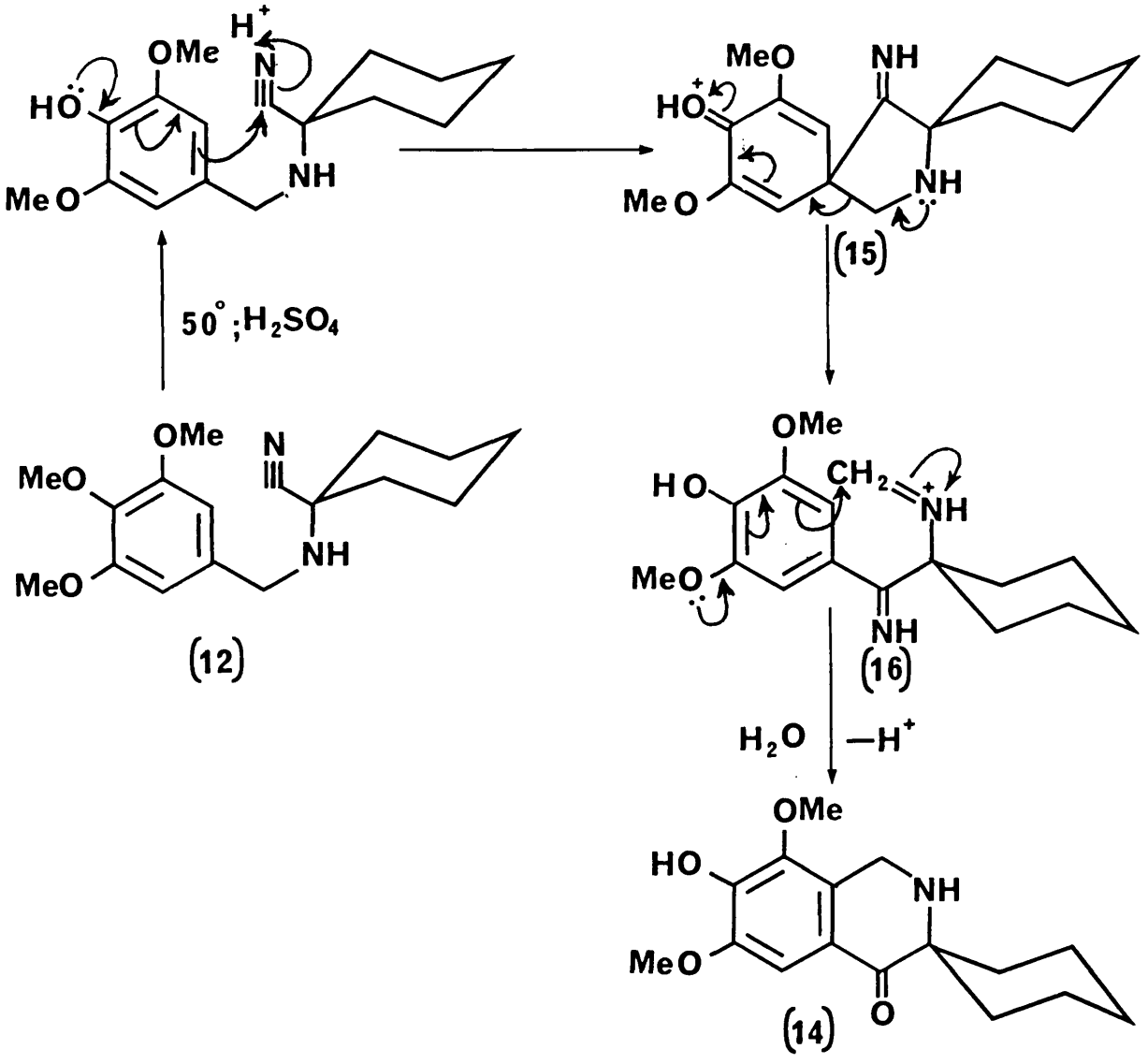
Scheme 20

A possible explanation for the formation of two products in cyclisation of the trimethoxy compound may lie in the fact that the central methoxy group cannot assume coplanarity with the aromatic ring due to steric hindrance. This prevents the central methoxyl group from exerting full activating mesomeric influence and classical cyclisation results.

At 50^{o} it is likely that O-demethylation of the central methoxy group occurs readily[60-63] and that the species undergoing cyclisation is in fact the 4-hydroxy-3,5-dimethoxy-benzylaminoacetonitrile. The smaller size of the hydroxyl

group now permits coplanarity with the aromatic ring, and the activating influence exerted by the group leads to electrophilic attack at C-1 with formation of the spiro-intermediate.

The formation of 2,3-dihydro-7-hydroxy-6,8-dimethoxy-isoquinolin-4(1H)-one-3-spirocyclohexane (14) is consistent with the formation of the spiro-intermediate (15) which undergoes rearrangement to an iminium ion (16) followed by Pictet-Spengler cyclisation (scheme 21).



Scheme 21

1.4.2 The influence of alternative intramolecular nucleophiles

a. The presence of a benzyl substituent

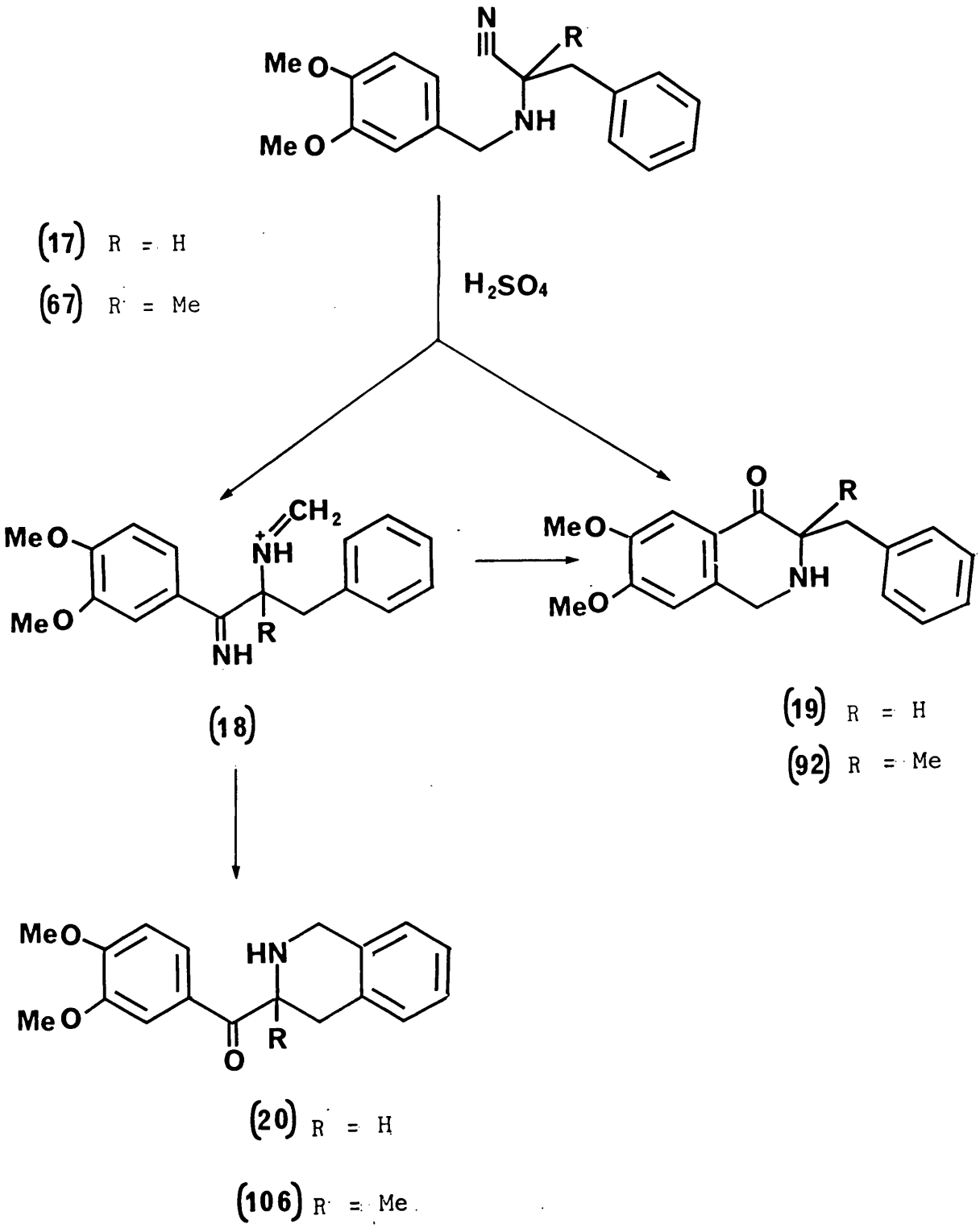
The utilisation of the nitrile route by Harcourt and co-workers[64] for the preparation of 3-benzylisoquinolines gave further evidence of the involvement of a spiro-intermediate.

In a preliminary report Harcourt, Taylor and Waigh[64] attempted the preparation of a 3-benzylisoquinolinone (92, R = Me,) by cyclisation of the aminonitrile (67, R = Me,) (scheme 22).

However, the sole product isolated was the 3-benzoyltetrahydroisoquinoline (106, R = Me). This observation is in accord with the production of an ion (18, R = Me), which undergoes Pictet-Spengler cyclisation involving that aromatic ring lacking the deactivating imino substituent.

A subsequent paper[65] confirms this but reports that the homologous nitrile (17, R = H) gave an equimolecular mixture of the 3-benzylisoquinolinone (19, R = H) and the dimethoxybenzoyltetrahydroisoquinolinone (20, R = H) (scheme 22). It is difficult to explain why a minor molecular modification of this nature should affect the course of cyclisation to this extent.

Although the formation of the dimethoxybenzoyltetrahydroisoquinolin (20) is consistent with the involvement of a spiro-intermediate, formation of the 3-benzylisoquinclinone (19) can occur by means of a classical cyclisation as originally postulated by Harcourt and Waigh[51] or via the



(17) R = H

(67) R = Me

(18)

(19) R = H

(92) R = Me

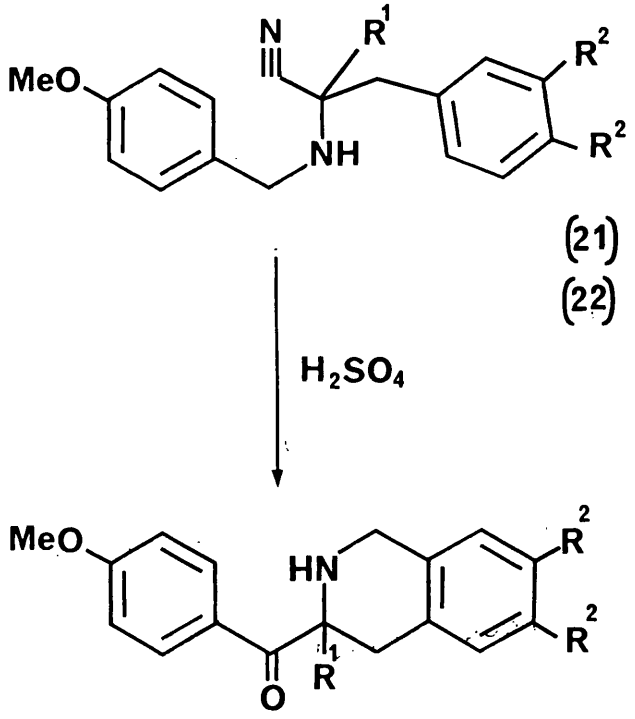
(20) R = H

(106) R = Me

Scheme 22

spiro-intermediate and iminium ion (18, R = H). Harcourt, Taylor and Waigh proposed that the iminium ion (18, R = H) thus formed could then be attacked by either of the aromatic rings (assuming that both aromatic rings are acting as competing nucleophiles) and hence cyclisation proceeding in either direction with equal ease.

Cyclisation of the aminonitrile (21) possessing a para methoxy substituent produced the 4-methoxybenzoyltetrahydroisoquinoline (23, R^1 = Me, R^2 = H, scheme 23) as the sole product in 73% yield. Here, the absence of a suitably orientated alkoxy group inhibits Pictet-Spengler cyclisation of the iminium ion to yield the isoquinolinone, cyclisation to the benzyl substituent occuring exclusively. It is interesting to note, however, that no imidazoline is formed.



(21) R^1 = Me; R^2 = H

(22) R^1 = Me; R^2 = OMe

		Yield (%)
(23)	R^1 = Me; R^2 = H	73
(24)	R^1 = Me; R^2 = OMe	30

Scheme 23

Contrary to expectations, increasing the reactivity of the aromatic ring (22, R^1 = Me, R^2 = OMe) did not result in an improved yield of tetrahydroisoquinoline (24). In fact the 6,7-dimethoxytetrahydroisoquinoline was isolated in only 30% yield. A possible reason is that sulphonation of the dimethoxy substituted ring could occur more readily, or that phenolic products are produced by O-demethylation. The authors do not mention any attempt to isolate these acidic products in this instance.

b. **The presence of a phenethyl substituent**

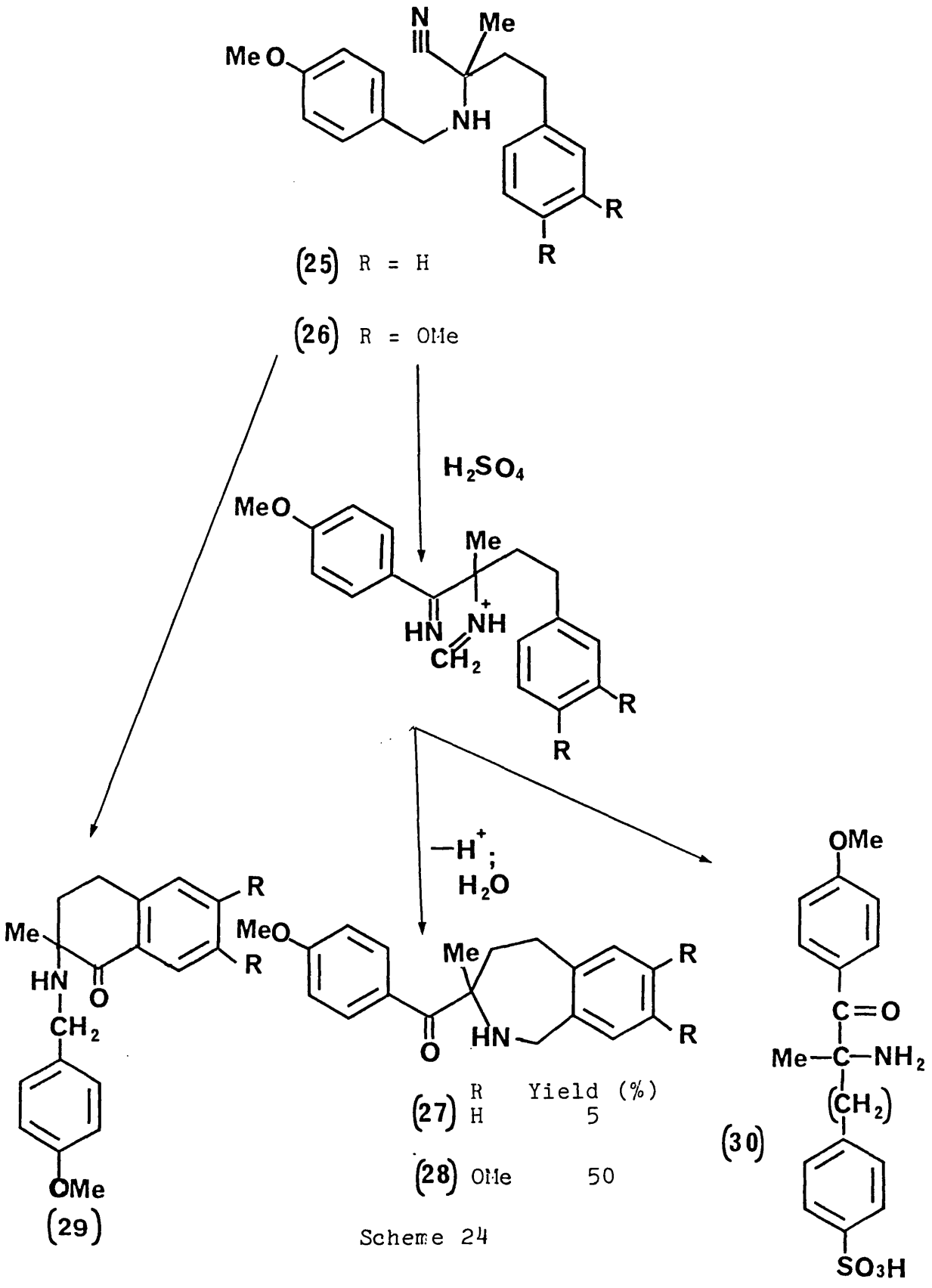
It is interesting to compare these results with those obtained when a phenethyl substituent is present as the nucleophilic site. For example, treatment of benzylamino-acetonitrile (25) with concentrated sulphuric acid at 50° or room temperature has been shown[65] to yield 2-benzazepine (27) in only 5% yield (scheme 24).

This is a reflection of the greater difficulty effecting Pictet-Spengler cyclisation to produce a seven-membered ring. The major product was reported to be a sulphonic acid (30).

However, in this instance, increasing the nucleophilic character of the aromatic ring (phenethyl substituent) by introduction of methoxy substituents, enabled the nitrile (26) to be converted to the 2-benzazepine (28) in 50% yield.

Here, sulphonation or O-demethylation does not appear to be of such significance as was proposed for the analogous cyclisation of the dimethoxybenzyl substituent in amino-nitrile (22).

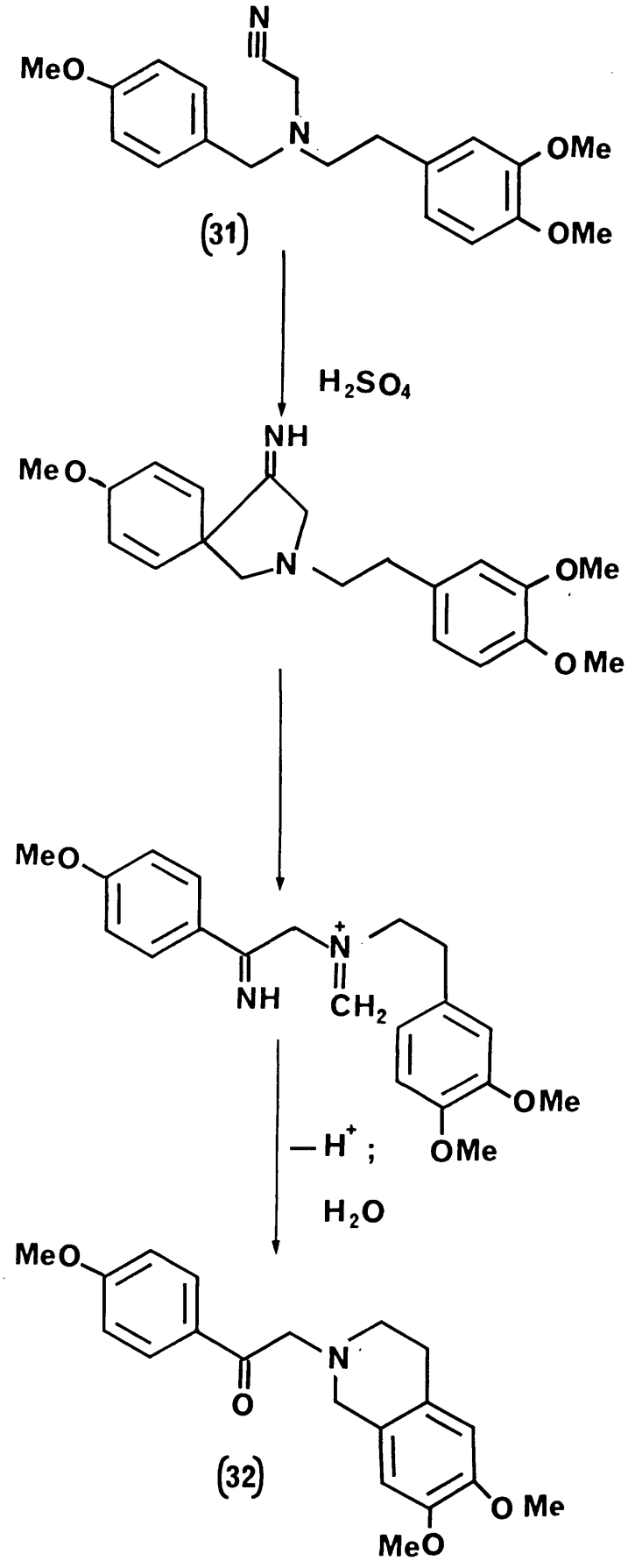
In addition, the alternative cyclisation of the aminonitrile to benzylamino substituted tetralone (29) was not observed.



Scheme 24

Further evidence for the occurrence of spiro-intermediate is seen in the cyclisation of 2-N-(3,4-dimethoxyphenethyl)-4-methoxybenzylaminoacetonitrile (31) which gave 1,2,3,4-tetrahydro-6,7-dimethoxy-2-(4-methoxyphenacyl) isoquinoline (32) in 33% yield (scheme 25). This again demonstrates the ability of the iminium ion to cyclise by interaction with an alternative nucleophile when one is present.

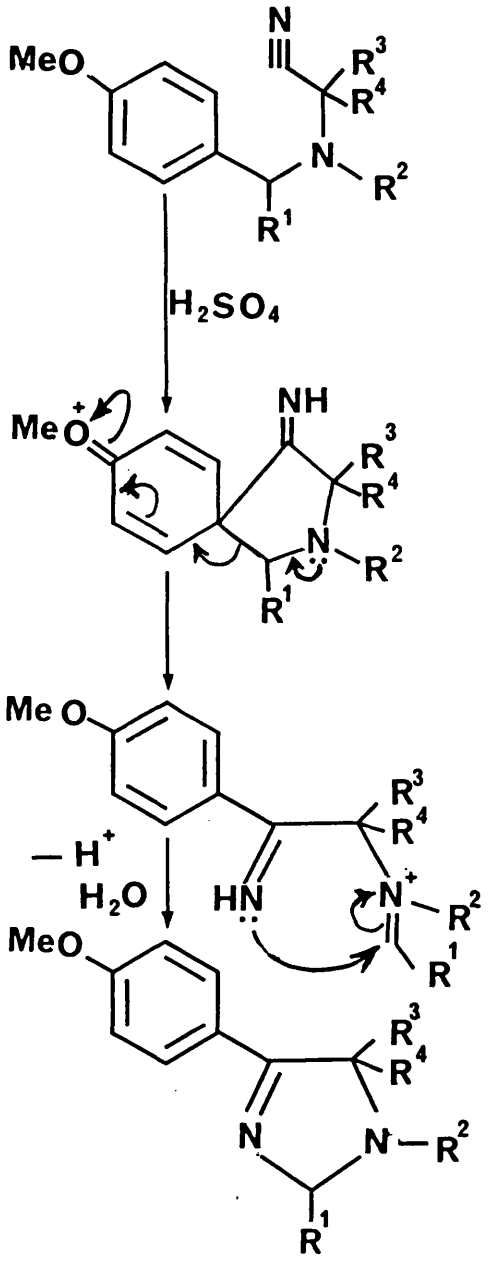
The low yield of the product may be due to O-demethylation resulting in phenolic products, which the authors did not attempt to isolate. The product was fully characterised (in addition to satisfactory spectroscopic data) by an unambiguous synthesis from the 1,2,3,4-tetrahydro--6,7-dimethoxyisoquinoline and 4-methoxyphenacyl bromide.


N
MeO
N
OMe
OMe
(31)
H_2SO_4
NH
MeO
N
OMe
OMe
MeO
NH
N
CH_2
OMe
OMe
$-H^+$;
H_2O
MeO
O
N
(32)
O Me
MeO

Scheme 25

Cyclisation of 4-methoxybenzylaminoacetonitriles in concentrated sulphuric acid has been shown to yield (in the absence of an alternative nucleophile) the 3-imidazolines.

Harcourt, Taylor and Waigh[66] have postulated that the reaction proceeded via electrophilic attack *para* to a C4-methoxyl substituent, resulting in a spiro-intermediate, which rearranges to an iminium ion. The lack of suitable electron density in the *ortho* position of an aromatic nucleus and the absence of an alternative nucleophile allows an attack by the imino group on the iminium ion resulting in the 3-imidazoline (scheme 26).



$R^3 = R^4 =$ alkyl

Scheme 26

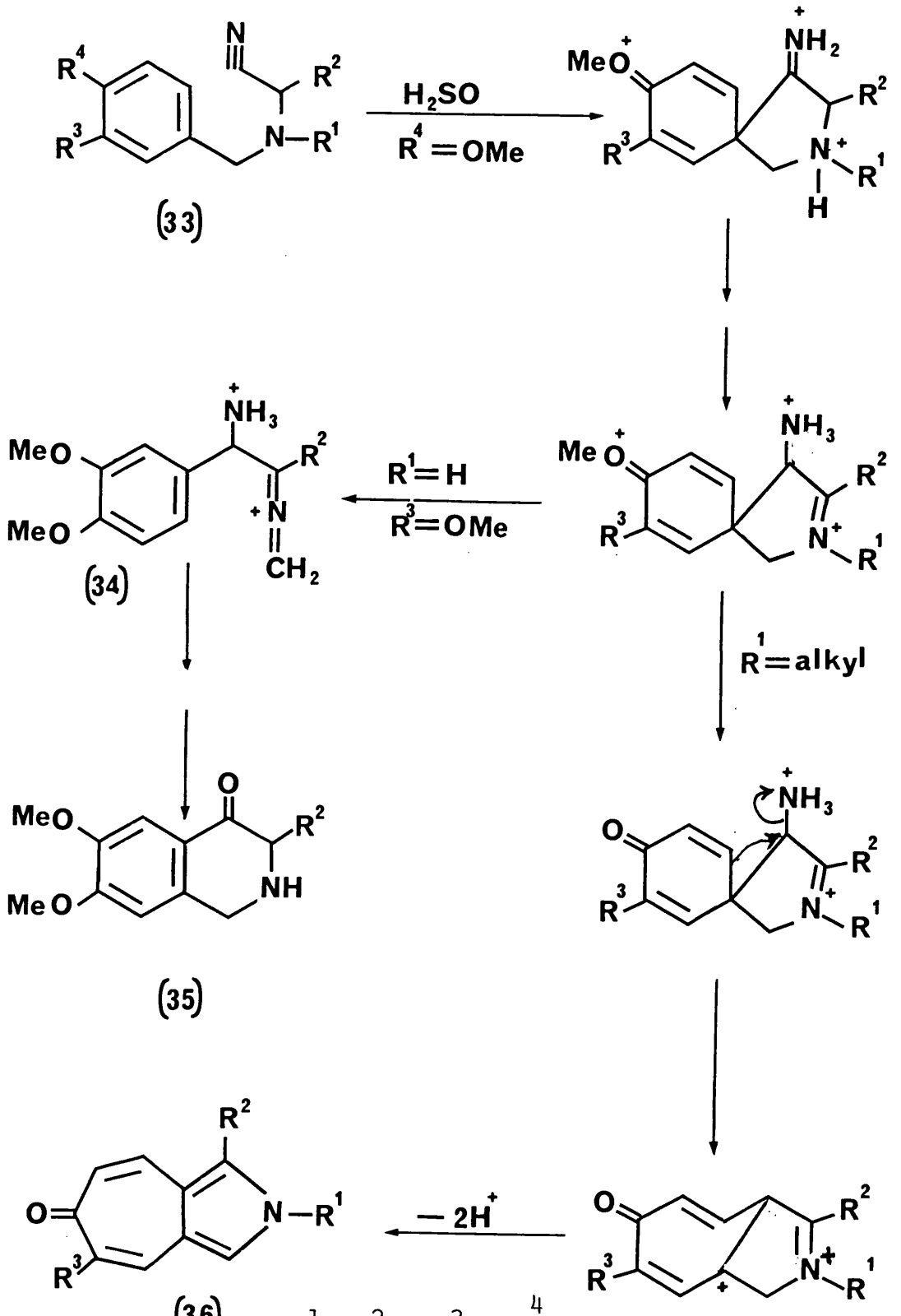
This approach to 3-imidazolines was later employed by Euerby and Waigh[67] who used the methylthio group as an activating substituent, which if desired, could be removed from the final product by reductive desulphurisation.

Waigh[68] has also reported that cyclisation of N-alkyl benzylaminonitriles (33) using concentrated sulphuric acid gave cyclohepta [c]-pyrrol-6(2H)-ones (36) instead of the isoquinolinones (scheme 27).

The author has explained this difference in behaviour by considering the spiro-intermediate and postulated that under very strongly acidic conditions both nitrogen atoms are protonated, with the possibility of tautomerism to give the most suitable conjugated iminium salt. This would then undergo cleavage (R^1 = H) to form iminium ion (34) followed by Pictet-Spengler cyclisation to yield isoquinolinone (35).

However, it has been proposed that when R^1 = alkyl, this path is blocked and (as claimed by the author), the longer life of the spiro-intermediate leads to its O-demethylation followed by a 1,2-shift with elimination of ammonia resulting in the cyclohepta [c] pyrrol-6(2H)-one.

In view of the present work discussed in this thesis, it is highly unlikely that a longer life time of the spiro-intermediate is necessary for the O-demethylation. It is apparent from the present work that O-demethylation is temperature dependent.



	R^1	R^2	R^3	R^4
a	Me	Ph	OMe	OMe
b	Me	DMP	OMe	OMe
c	Me	Ph	H	OMe

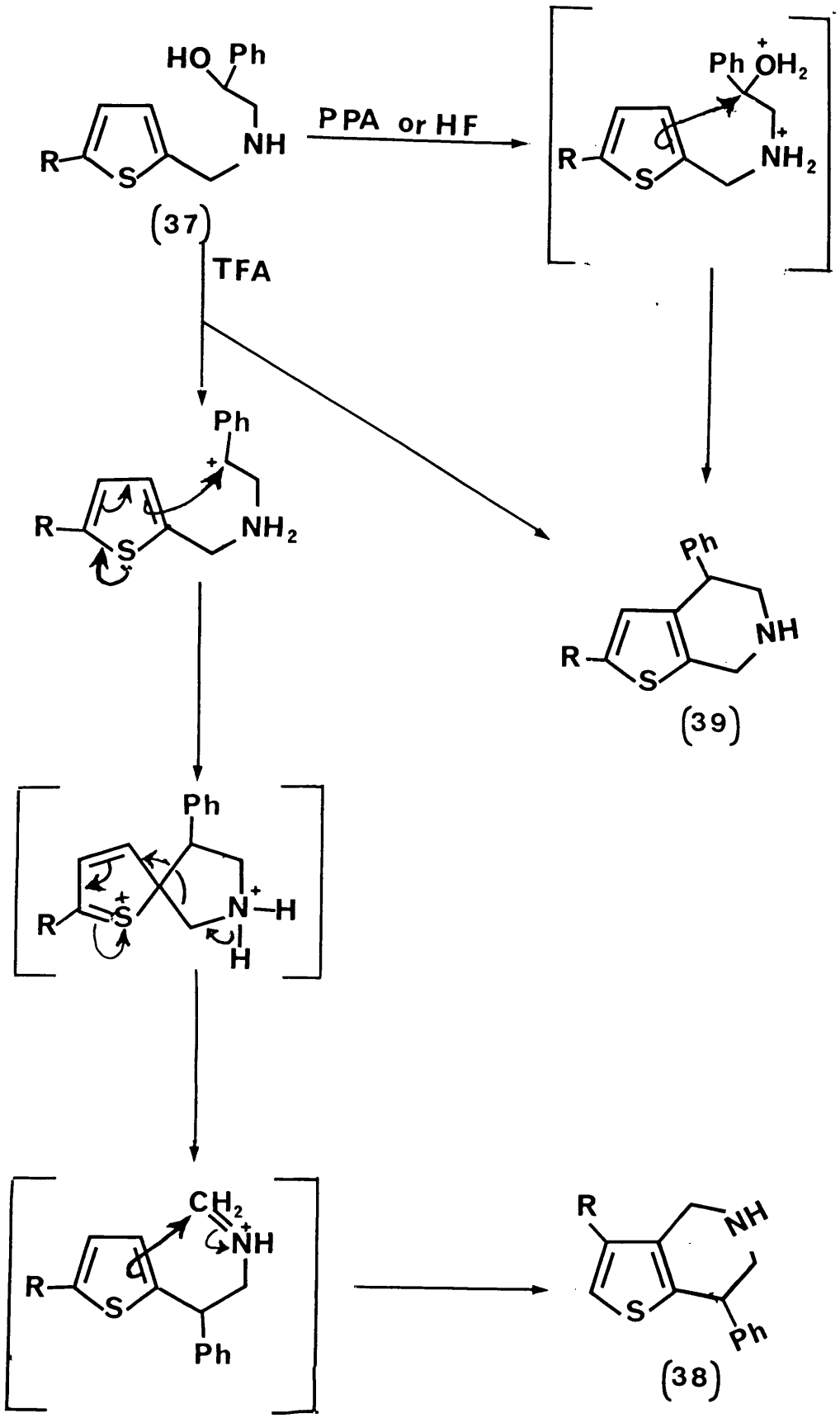
DMP = 3,4-$(MeO)_2C_6H_3$

Scheme 27

The occurrence of the spiro-intermediate in organic reactions is not uncommon. Many examples may be found in the literature[69-84] and cover a wide range of reactions involving carbocation, carbanion and free radical intermediates. These are discussed in an excellent review by Newman[85].

More recently Waigh has reported further examples in heterocyclic chemistry involving the preparation of thienopyridines[86] and tetrahydroisoquinoline[87].

Thus cyclisation of N-(2-hydroxyphenethyl)-2-aminoethylthiophens (37) with trifluoroacetic acid have been shown to yield the thienopyridines (38,39). The formation of thienopyridine (38) indicated that cyclisation proceeded via the spiro-intermediate, whereas the formation of the isomeric thienopyridine (39) suggests that the classical cyclisation cannot be precluded in this reaction (scheme 28).

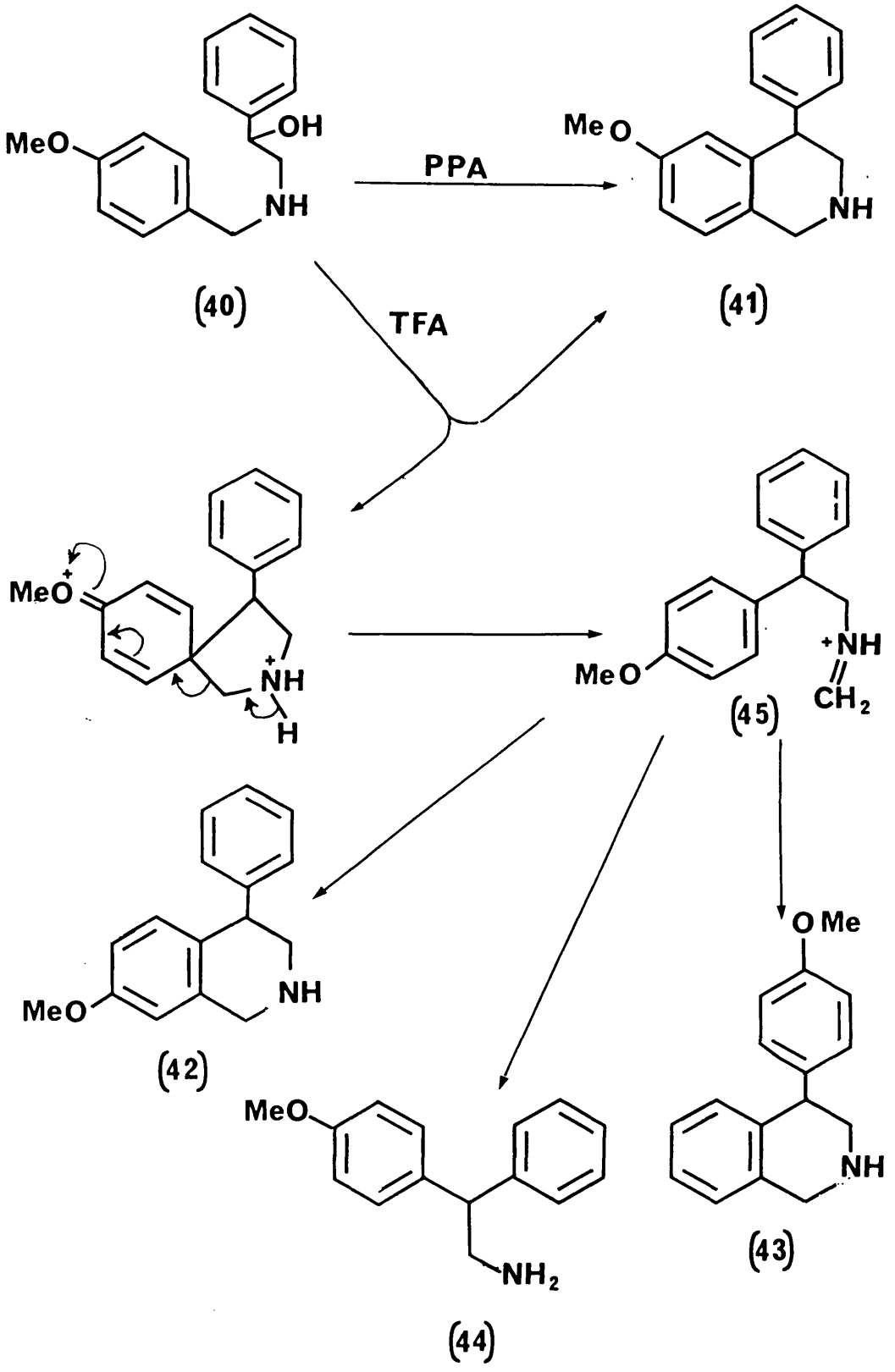


Scheme 28

Similarly, Euerby and Waigh[87] have reported the occurrence of the spiro-intermediate in cyclisation of N-(4-methoxybenzyl)-1-phenyl-2-aminoethanol (40) using trifluoroacetic acid.

A mixture of products in total yield of 88% w[illegible] obtained. This was made up of unrearranged (via classical cyclisation) tetrahydroisoquinoline (41, 21%), rearranged (via spiro-intermediate) products (42 and 43) inatotal yield of 12%, which the authors failed to separate. The major product from treatment with trifluoroacetic acid was reported to be diarylamine (44, 67%) which the authors claimed arose from the hydrolysis of the imine (45) (scheme 29).

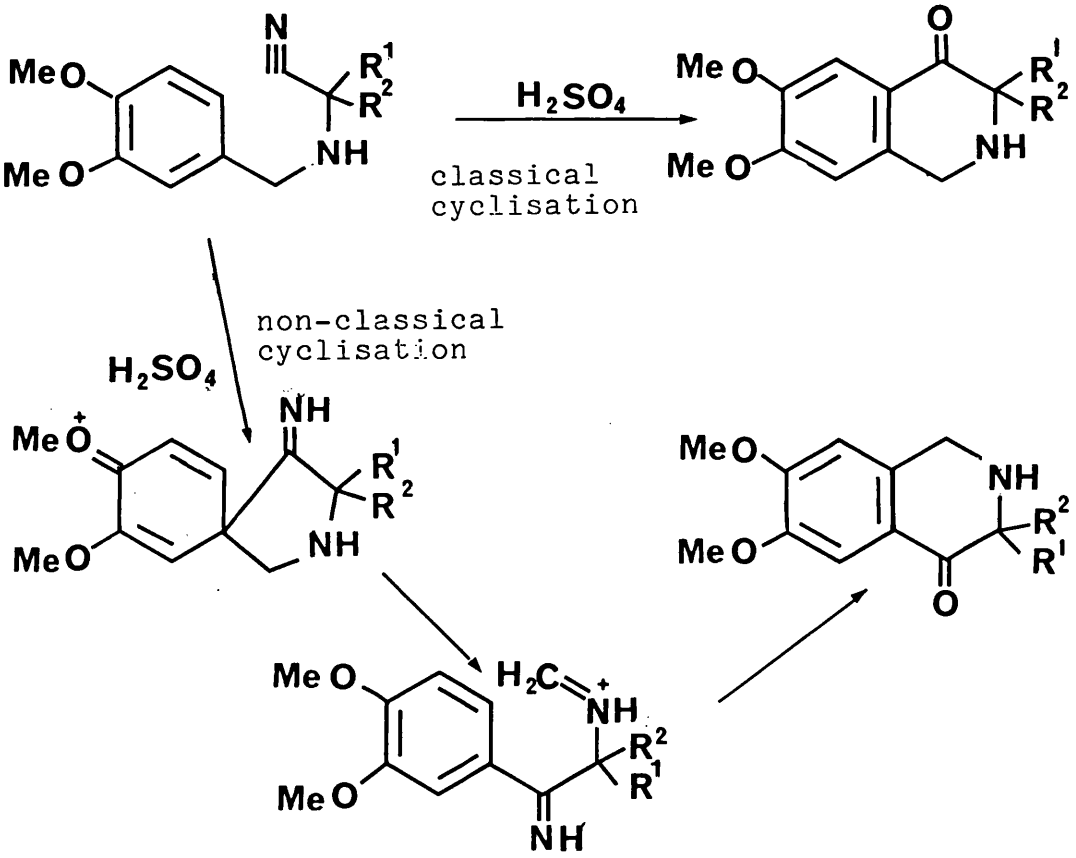
However, cyclisation with polyphosphoric acid gave exclusively the tetrahydroisoquinoline (41).


MeO
OH
NH
PPA
Me O
NH
(40)
TFA
(41)
MeO
NH
H
+NH
MeO
CH2
(45)
MeO
NH
(42)
O Me
NH
MeO
NH2
(43)
(44)

Scheme 29

1.4.3 Cyclisation of ethoxymethoxybenzylaminoacetonitriles

Though the above work had provided ample evidence of the involvement of a spirocyclic intermediate in the cyclisation of a range of benzylaminonitriles, it was yet to be proven that the simple 3,4-dimethoxybenzylaminoacetonitriles such as those used in the original investigation (see scheme 19, page 27) were capable of behaving in such a manner. In these instances, the same product is obtained whether classical or spirocyclic intermediates are involved (scheme 30).



Scheme 30

Thus in a preliminary investigation Nasir[88] prepared the ethoxymethoxybenzylaminoacetonitrile (59) obtained by standard procedures from vanillin and the isomeric amino-nitrile (60, derived from isovanillin) as suitable subjects for assessing the involvement of a spirocyclic intermediate. Here, clearly the orientation of the alkoxy substituents in the resulting isoquinolinone will be dependent upon the mechanism of cyclisation.

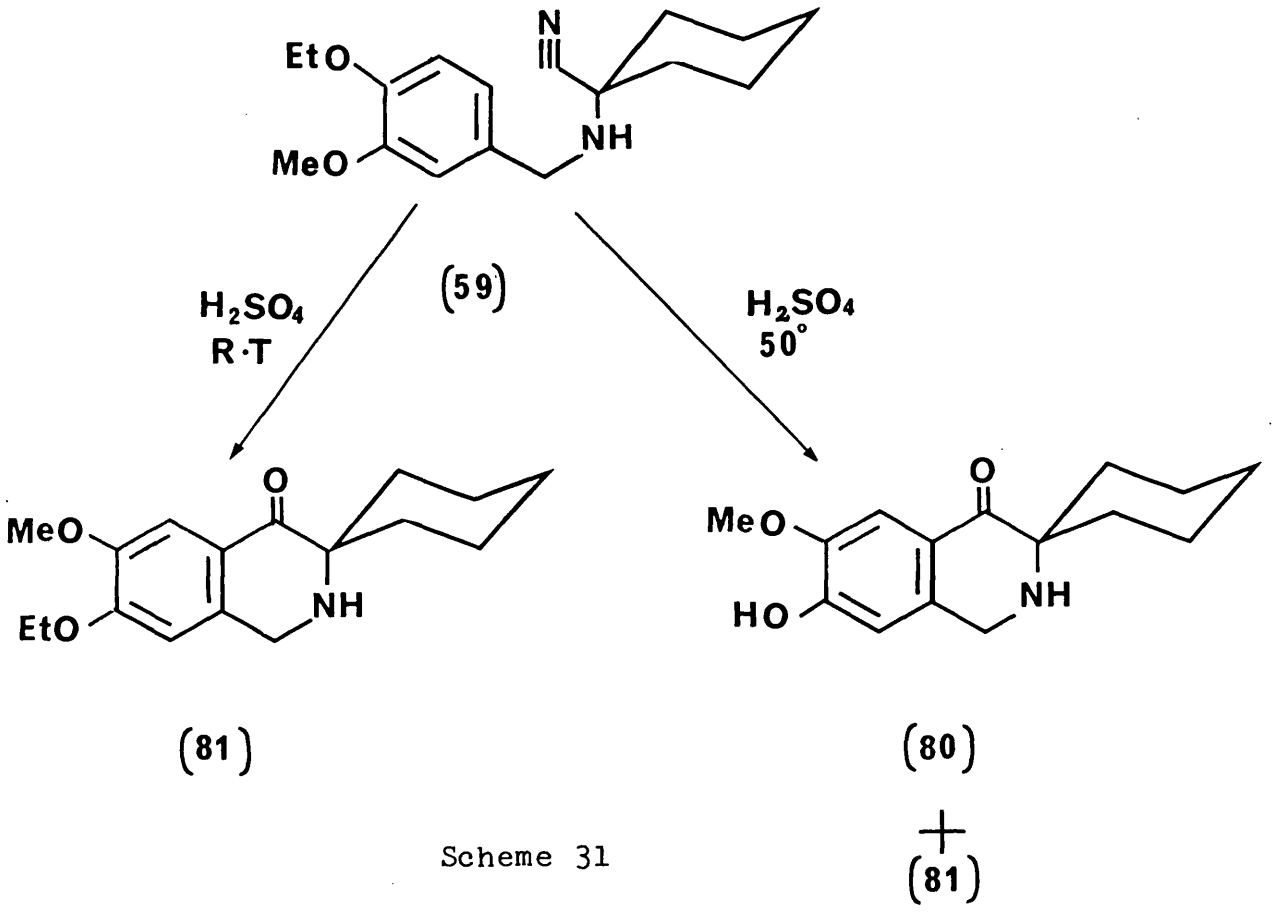
Nasir's procedure involved cyclisation of these nitriles at room temperature (R.T.) and 50°, the isolation of crude dialkoxy and crude phenolic isoquinolinones, and fractional crystallisation of these crude products.

The orientation of the C6- and C7- oxygenated substituents in these products was established by a combination of techniques. For phenolic products, the orientation of the hydroxy group could be ascertained from the bathochromic shift data derived from ultra-violet spectra and also by observation of upfield shifts induced in the ^{1}H n.m.r. spectra by addition of NaOD. The technique described below was also used as confirmation.

For the dialkoxy isoquinolinones, the ^{1}H n.m.r. probe technique described by Waigh[89] was employed. This involved introduction of a benzyl-substituent at C4 (via a Grignard reaction) and observation of the strong shielding influence this had on the C5 proton and C6 alkoxy group.

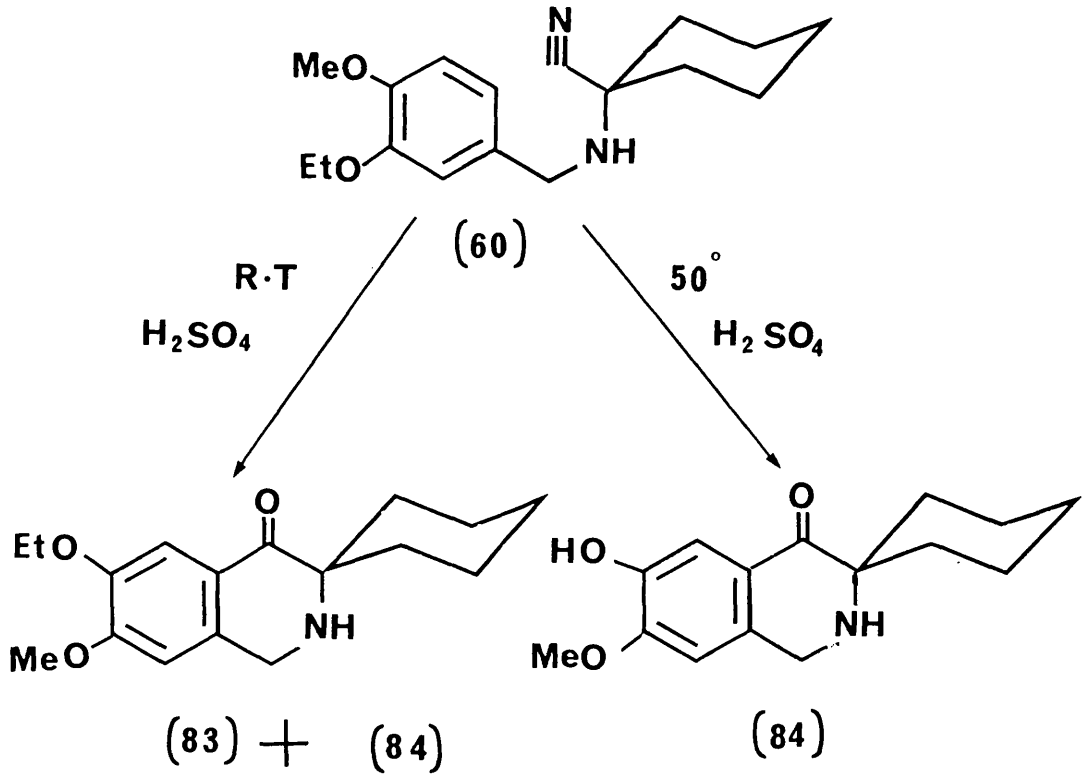
A further discussion of these techniques, which have become standard procedures in this investigation may be found in part II of this thesis (page 48).

The results obtained by Nasir[88] are summarised in scheme 31 and 32.



Scheme 31

At room temperature, no phenolic product was isolated but at 50° this was the major product obtained.



Scheme 32

At 50° only the phenolic product (84) was isolated, whereas at room temperature a mixture of phenolic and dialkoxy isoquinolinone was produced.

Thus all products isolated by Nasir have structures consistent with cyclisation involving the spiro-intermediate. However, since no attempt was made to fully characterise the composition of the crude reaction products (dialkoxy and phenolic isoquinolinones), the classical cyclisation could not be precluded. Therefore, the initial aim of the work presented in this thesis was to ascertain whether cyclisation of these dialkoxybenzylaminonitriles proceeded exclusively via the spirocyclic mechanism, or otherwise.

PART II

DISCUSSION OF RESULTS

2.0.1 Preparation of Benzylaminoacetonitriles

Preparation of the benzylaminoacetonitriles from the appropriate benzaldehyde via the oxime, benzylamine and subsequent Strecker reaction, proceeded smoothly with overall yields of 55-60% in the majority of cases (pages 161-163).

2.0.2 Cyclisation of Benzylaminoacetonitriles

The aminonitriles were treated with concentrated sulphuric acid (98%) for 4 hours at -10°, room temperature (R.T.) and 50°. The reaction mixture was then poured onto iced water, stirred for 45 minutes and then basified with 5N sodium hydroxide solution. Extraction with chloroform gave the crude alkoxy product(s).

Reacidification of the extracted aqueous phase, followed by basification with sodium hydrogen carbonate gave, after thorough extraction with chloroform, the crude phenolic product(s).

Thin layer chromatography (t.l.c) was used routinely to analyse the crude products.

The strength of sulphuric acid used for cyclisations was checked periodically to ensure that the content of sulphuric acid did not fall below 98% w/w.

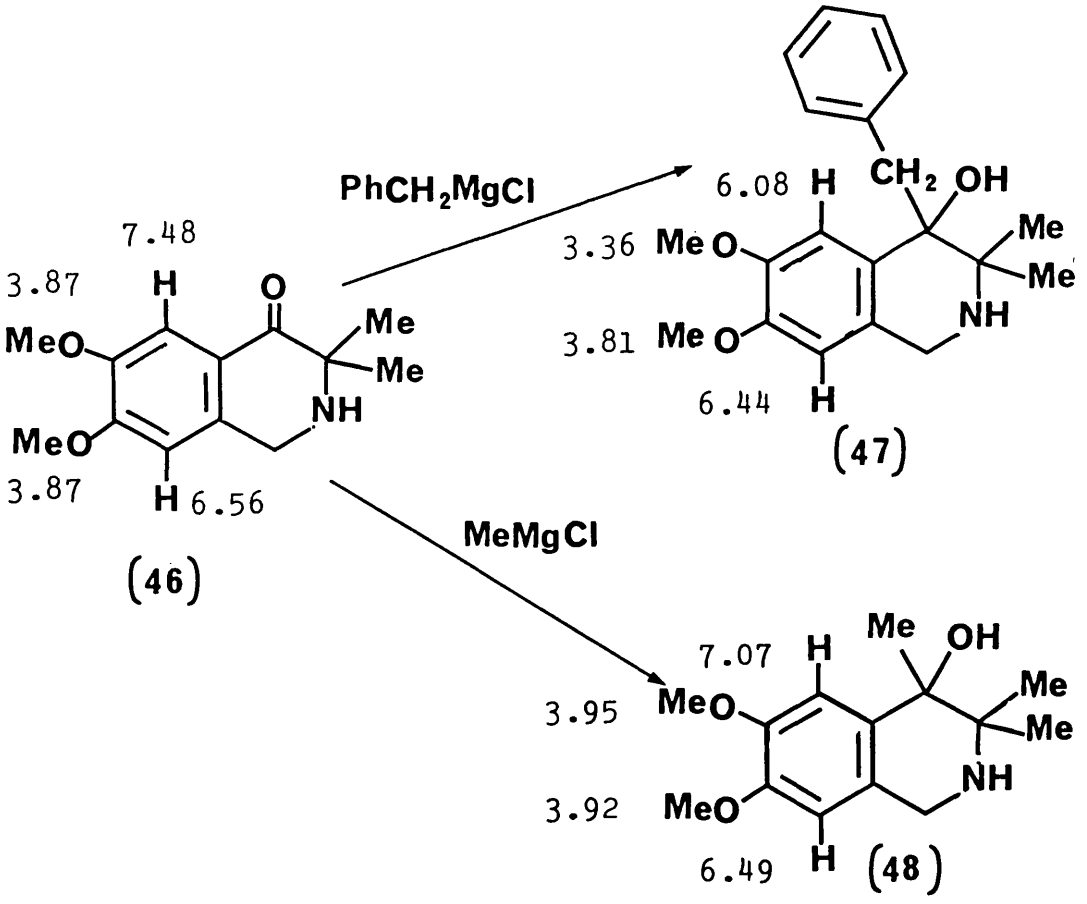
2.0.3 Orientation of oxygenated substituents at C6 and C7

6,7-Dialkoxyisoquinolinones

4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines.

The orientation of the C6 and C7 substituents in the dialkoxyisoquinolinones could not be determined directly by spectroscopy. However, this difficulty was overcome by Waigh[89], who reported that upon introduction of a benzyl group at the C4 position, (via a Grignard reaction) the signals due to the C5-proton and C6-substituent underwent an upfield shift.

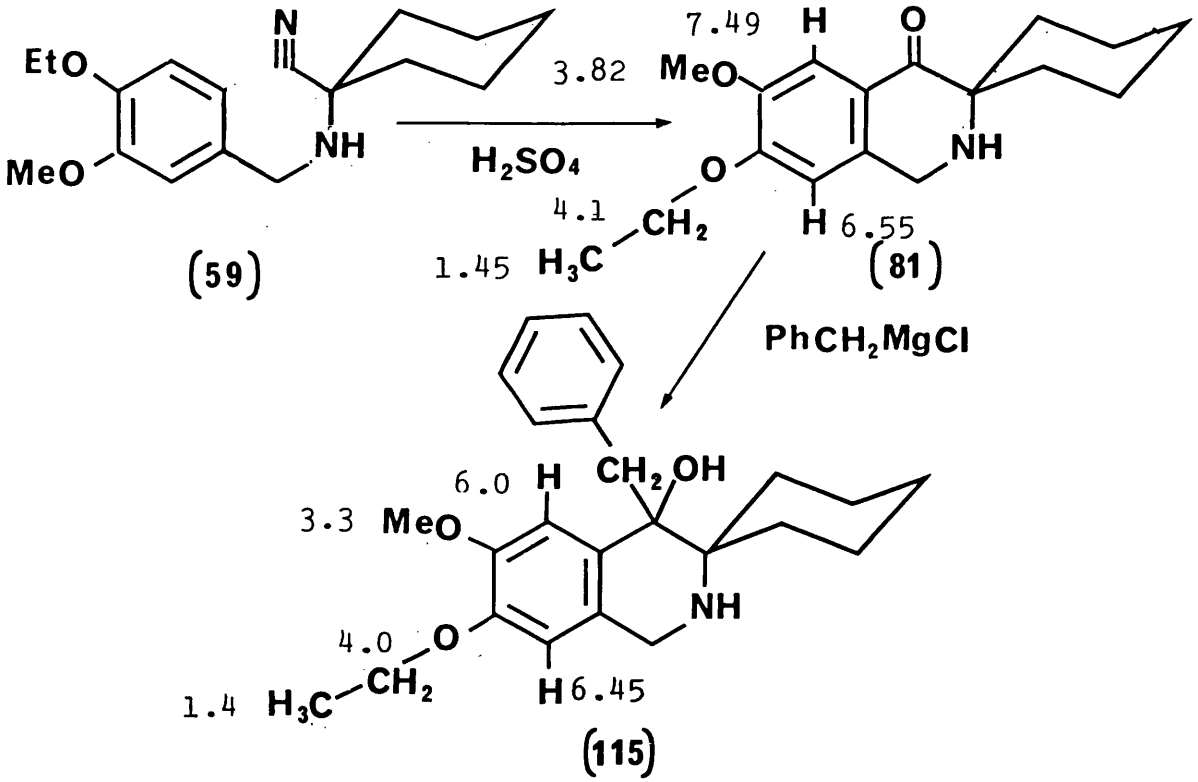
The relevant chemical data (δ ppm) are shown for the isoquinolinone (46) and benzylderivative (47) in scheme 33.



Scheme 33

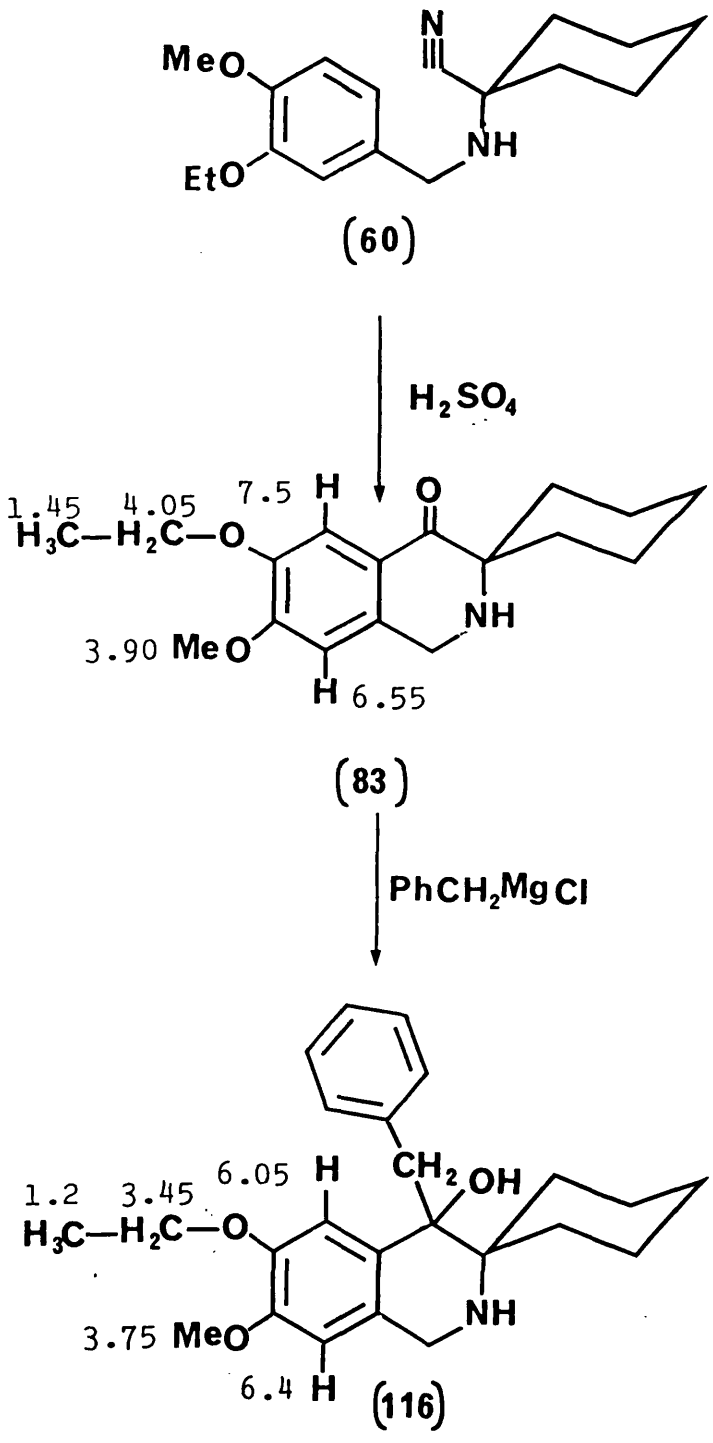
Waigh has also prepared the 4-methyl analogue (48) to ensure that the effect is attributable to the anisotropic effect and not due to the 4-alkyl substituent in any other way. This approach has also been employed by Nasir[88] in the determination of the orientation of the C6 and C7 substituents in the isomeric ethoxymethoxyisoquinolinones (derived from cyclisation of the isomeric ethoxymethoxybenzylaminoacetonitriles).

Thus reaction of the dialkoxyisoquinolinone (81) with benzylmagnesium chloride has been shown to yield the 4-benzyl-4-hydroxytetrahydroisoquinolinone (115), for which the chemical shift of the methoxy substituent shows that it is located at the C6 position. The resultant chemical shifts (δ ppm) are shown in scheme 34.



Scheme 34

Similarly, Nasir has reported that the dialkoxyisoquinolinone (83) obtained from cyclisation of the isomeric aminonitrile (60) had the ethoxy group substituted at the C6 position (scheme 35).



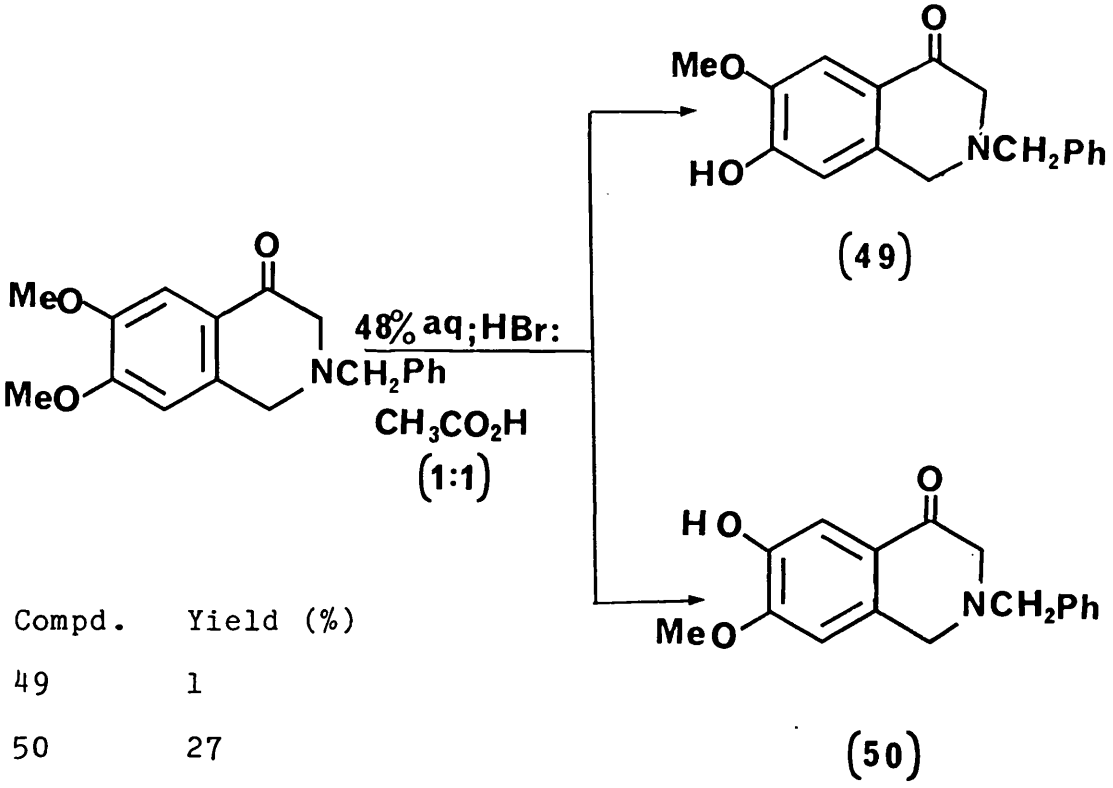
Scheme 35

Phenolic isoquinolinones.

a. Ultra-Violet Spectroscopy

Lemon[90] has reported that in alkaline solution the absorption bands in the ultra-violet spectra of a number of hydroxy aldehydes and ketones shifted to longer wavelength, and also the intensity of the absorption of the long wave bands was increased, with the exception of meta-hydroxybenzyldehydes. The effects are greater when the phenolic hydroxyl group was para to the carbonyl function.

This principal has been utilised by Grethe and co-workers[91] to determine the orientation of the C6 and C7 substituents in hydroxymethoxyisoquinolinones (produced by the selective O-demethylation of 6,7- and 7,8-dimethoxyisoquinolinones scheme 36).



Compd.	Yield (%)
49	1
50	27

Scheme 36

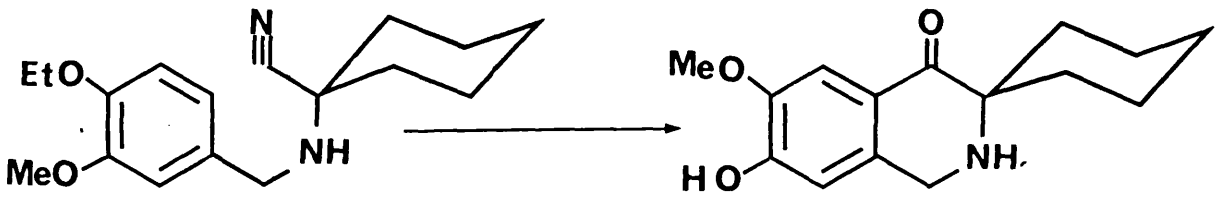
Thus in absolute ethanol the absorption spectra of both compounds were similar, but in basic medium (sodium acetate in absolute ethanol) the 6-hydroxy-7-methoxyisoquinolinone (50) showed no dissociation and hence no significant change in the spectrum was observed. However, the phenolic isoquinolinone (49) exhibited the bathochromic shift to longer wavelength, indicating the anion formation at the C7-hydroxy function.

The bathochromic shift seen in the ultra-violet spectra of these phenolic isoquinolinones in basic medium is in accord with the fact that all phenolic hydroxyl groups (except for sterically hindered) are dissociated under such conditions[92].

Recently this technique has been employed by Nasir[88] in the determination of the orientation of hydroxymethoxy-isoquinolinones isolated from cyclisation of the isomeric ethoxymethoxybenzylaminoacetonitriles (59 and 60).

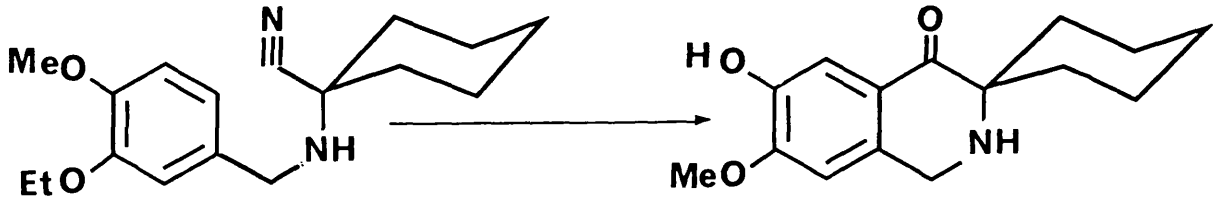
The ultra-violet spectra of these phenolic isoquinolinones were recorded in 95% ethanol and 0.01 M KOH in 95% ethanol, and were compared with the ultra-violet spectra of vanillin and isovanillin as reference compounds.

The results obtained by Nasir are shown in scheme 37 and spectra shown in figures 1-4. These results clearly show that the phenolic isoquinolinone obtained from cyclisation of the 4-ethoxy-3-methoxybenzylaminoacetonitrile has the same orientation of the hydroxy and carbonyl groups as that present in vanillin. Therefore the hydroxyl group is located at C7.



(59) (80)

By comparison, the hydroxymethoxyisoquinolinone (84) obtained from cyclisation of the 3-ethoxy-4-methoxybenzyl-aminoacetonitrile (60) has the same orientation of the hydroxy and carbonyl group as that present in iso-vanillin.



(60) (84)

	Neutral			Alkaline		
	λ_{max}	$E^{1\%}_{1cm}$	logϵ	λ_{max}	$E^{1\%}_{1cm}$	logϵ
Vanillin*	310	720	4.04	353	1960	4.47
Isovanillin**	314	560	3.93	360	460	3.78
Phenolic isoquinolinone (80)	313	310	3.90	350	880	4.36
Phenolic isoquinolinone (84)	3.9	280	3.86	365	200	3.71

* Lit[93] quotes logϵ 4.03 (EtOH), 4.48 (KOH in EtOH)

** Lit[93] quotes logϵ 3.94 (HCl in H_2O), 3.78 (NaOH in H_2O)

Scheme 37

Fig 1

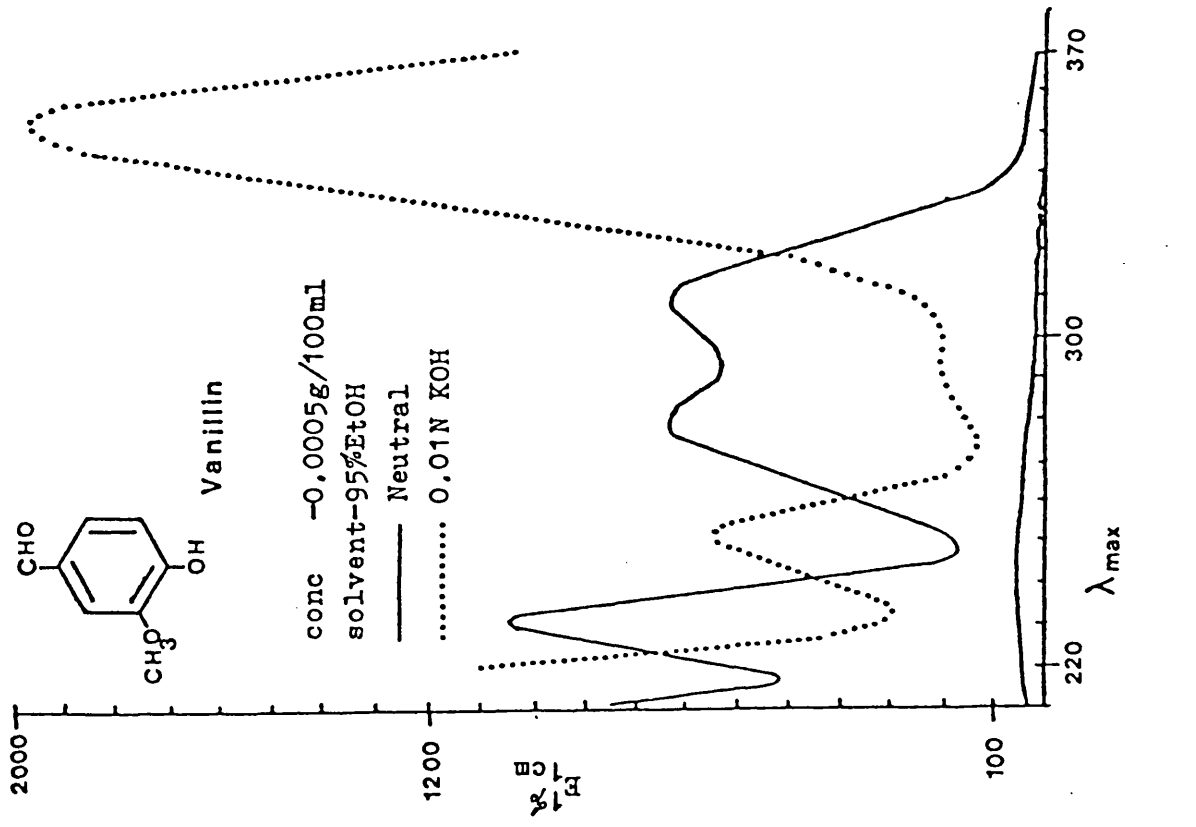

Vanillin
CHO
OH
CH_3O
conc -0.0005g/100ml
solvent-95%EtOH
Neutral
0.01N KOH
$E^{1\%}_{1cm}$
2000
1200
100
220
300
370
λ_{max}

Fig 2

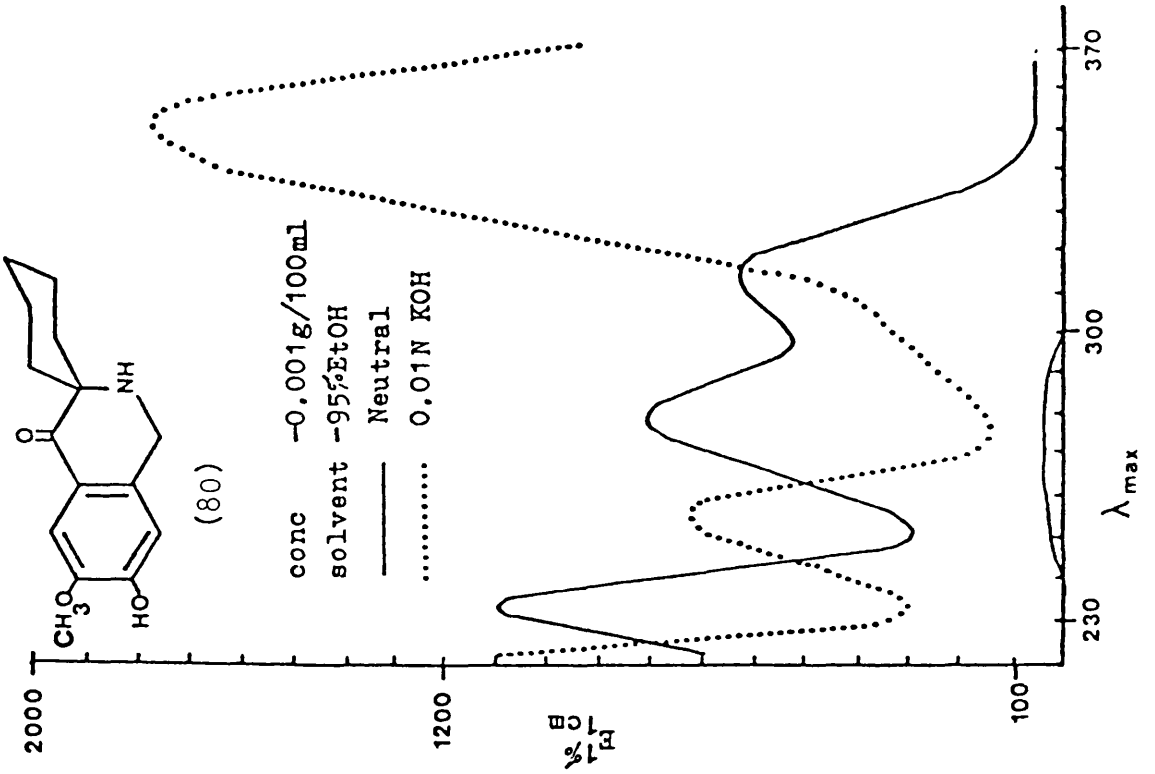

(80)
NH
O
CH_3O
HO
conc -0.001g/100ml
solvent -95%EtOH
Neutral
0.01N KOH
$E^{1\%}_{1cm}$
2000
1200
100
230
300
370
λ_{max}

Fig 3

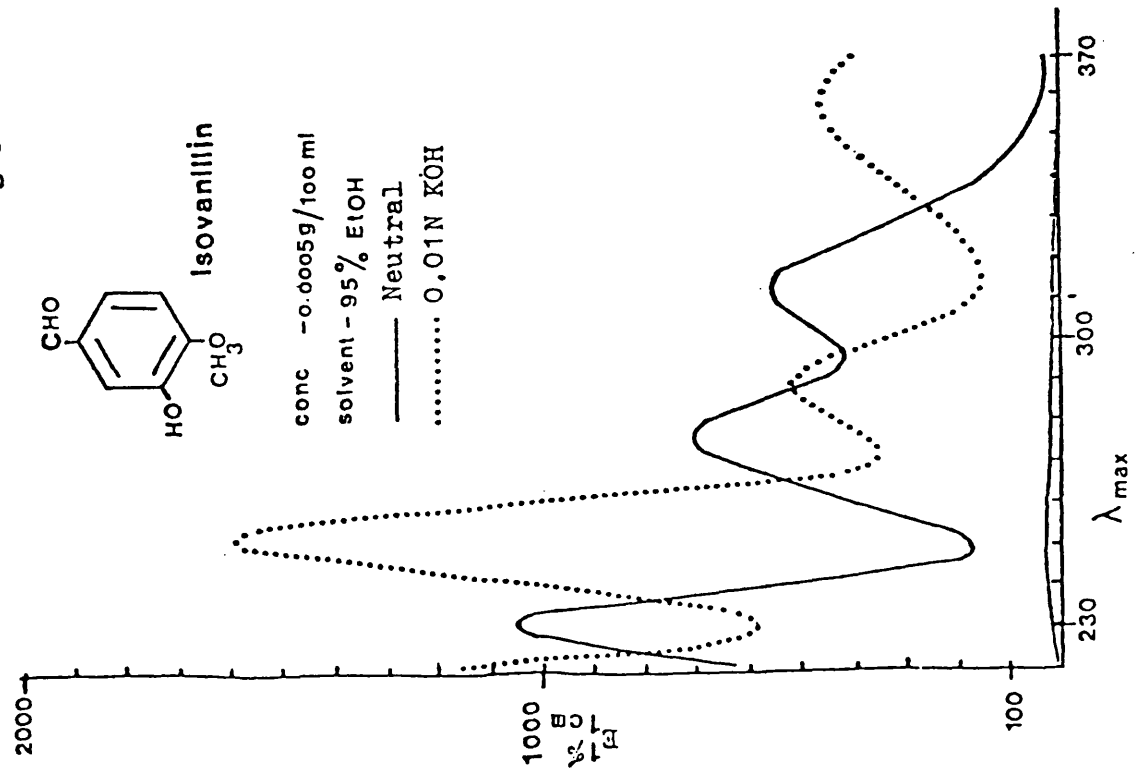
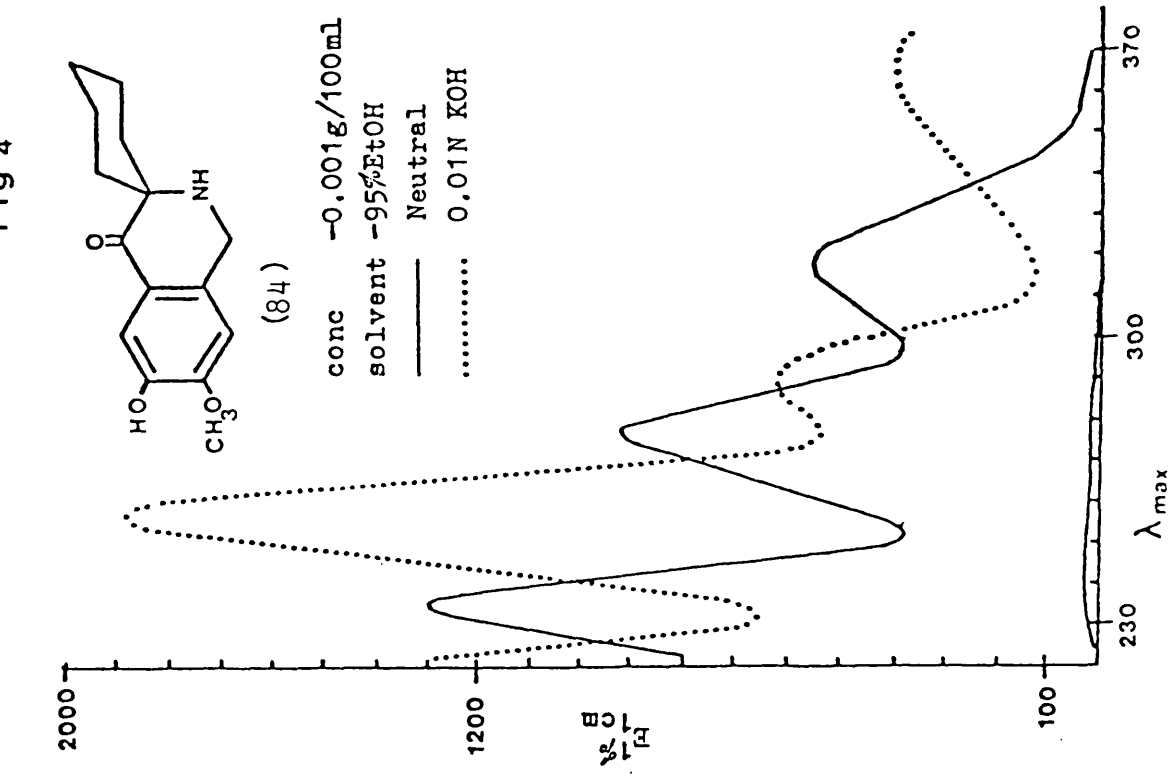

Isovanillin
CHO
HO
CH_3O
conc -0.0005g/100 ml
solvent - 95% EtOH
Neutral
0,01N KOH
2000
1000
100
$E^{1\%}_{1cm}$
230
300
370
λ_{max}

Fig 4


(84)
HO
CH_3O
NH
O
conc -0,001g/100ml
solvent -95%EtOH
Neutral
0,01N KOH
2000
1200
100
$E^{1\%}_{1cm}$
230
300
370
λ_{max}

b. ^{1}H.n.m.r. - NaOD shift technique

Brossi and co-workers have used this technique to establish the orientation of substitution at C6 and C7 in the alkaloid cherylline[94].

The method involves addition of a few drops of NaOD in D_2O, which has a marked affect on the chemical shifts of the aromatic proton signals. The enhanced shielding effect produced on converting a phenol to its anion is much greater at the ortho and para position than at the meta position.

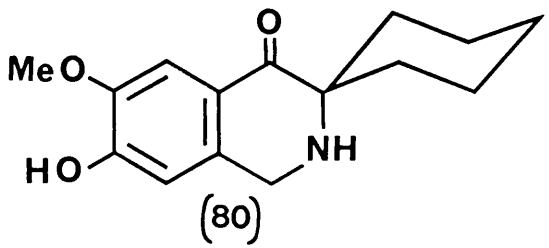
The procedure was recently employed by Nasir[88] to determine the orientation of the hydroxy and methoxy groups in the 6,7-disubstituted phenolic isoquinolinones.

Thus ^{1}H.n.m.r. spectrum of 7-hydroxy-6-methoxyisoquinolinone (80) (obtained from 4-ethoxy-3-methoxybenzylaminoacetonitrile, 59) in DMSO shows two singlets at δ 7.35 and 6.6 ppm due to the C5-H and C8-H protons respectively.

However, on addition of 2-3 drops of NaOD in D_2O both signals are shifted to higher field (δ7.05 and 5.96 ppm), representing a shift of 30 Hz and 64 Hz respectively and confirming the location of the hydroxyl group at C7 (figure 5).

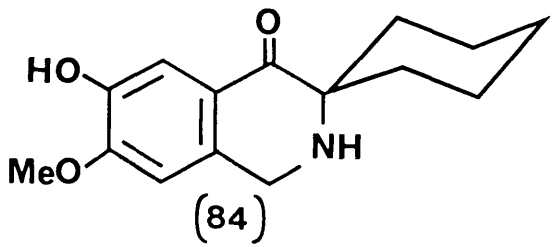
In the isomeric 6-hydroxy-7-methoxyisoquinolinone (84) (obtained from 3-ethoxy-4-methoxybenzylaminoacetonitrile, 60) the shift is less marked, possibly due to the anisotropic deshielding effect of the C4 carbonyl on the C5 proton.

However, on treatment with NaOD in D_2O the C5-proton showed an upfield shift of 54 Hz and C8-proton 40 Hz, thus confirming the phenolic hydroxy group at C6 (figure 6).



(80)

Fig 5


O
HO
NH
MeO

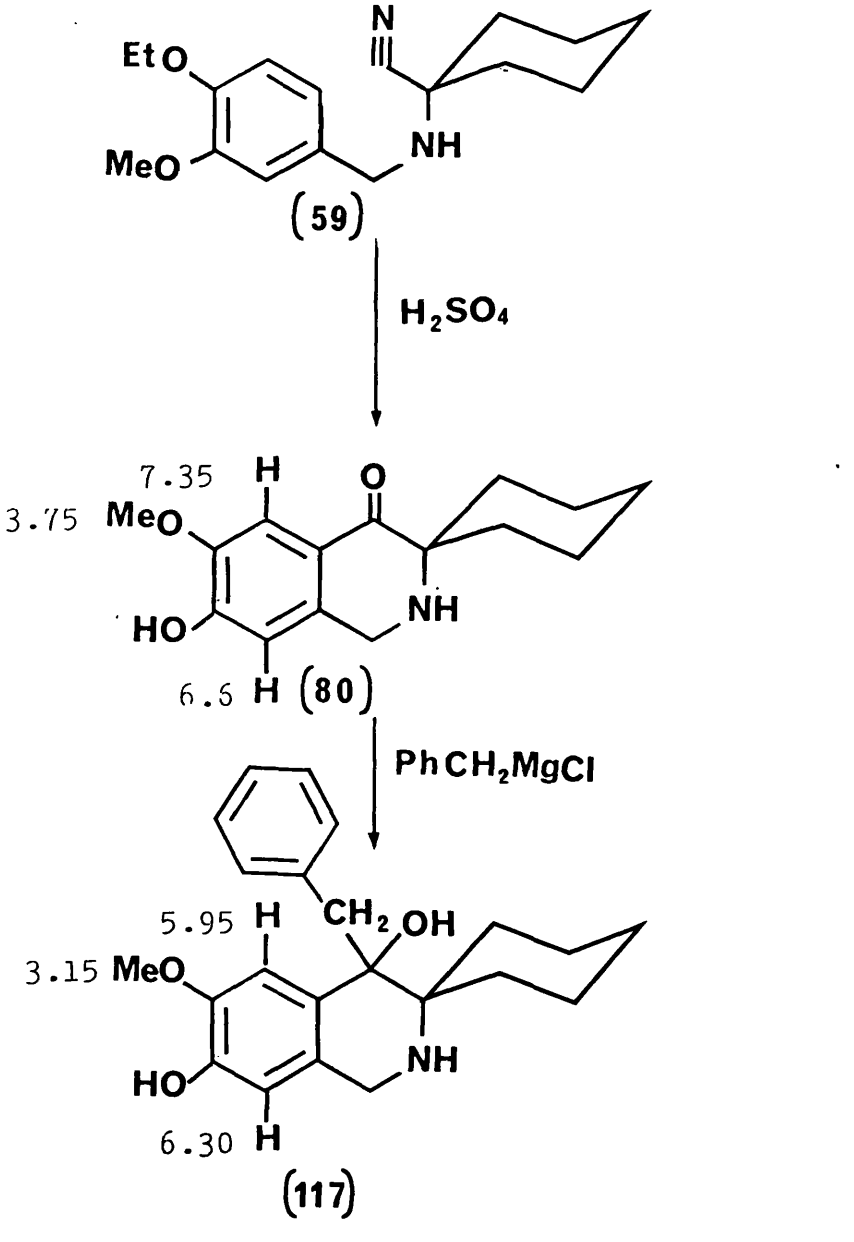
(84)

Fig 6

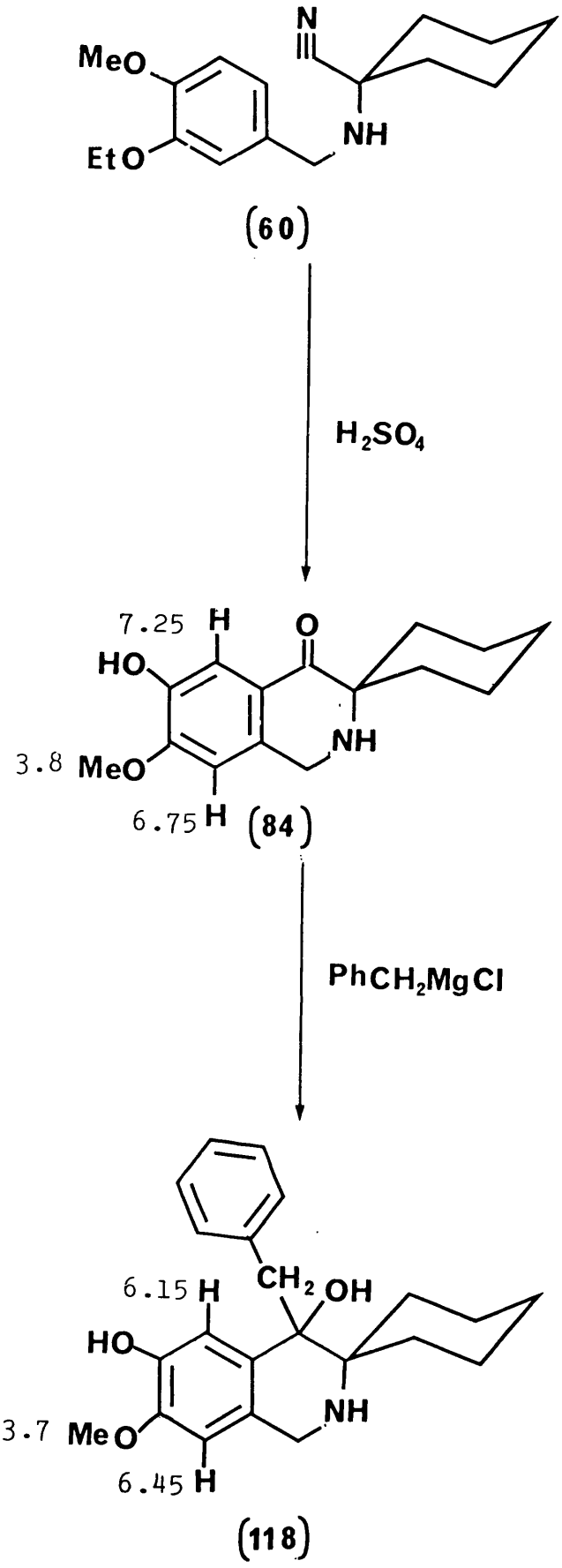
NaOD/D2O
added
deuterated
deuterated
TMS
10
9
8
7
6
5
4
3
2
1
0
δ (ppm)

c. 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines.

Further structural assignment of the phenolic isoquinolinones was ascertained by the introduction of the benzyl group at the C4 position. The results obtained by Nasir are shown in scheme 38 and 39, and confirm that the methoxyl group (in 80) is located at C6, whereas in (84) it is located at C7.



Scheme 38


N
MeO
EtO
NH
(60)
H_2SO_4
7.25
H
O
HO
NH
3.8
MeO
6.75
H
(84)
$PhCH_2MgCl$
CH_2
OH
6.15
H
HO
NH
3.7
MeO
6.45
H
(118)

Scheme 39

2.1.0 Preparation and cyclisation of 1-(3,4-dialkoxybenzyl-amino) cyclohexane carbonitriles

2.1.1 Preparation of 1-(3,4-dimethoxybenzylamino) cyclohexane carbonitrile (58) 1-(4-ethoxy-3-methoxybenzylamino) cyclohexane carbonitrile (59) and 1-(3-ethoxy-4-methoxy--benzylaminoacetonitrile (60)

The 3,4-dimethoxybenzylaminoacetonitrile (58) and the isomeric ethoxymethoxybenzylaminoacetonitriles (59,60) were derived in excellent yield from verataldehyde, vanillin and isovanillin respectively as previously described[51,88].

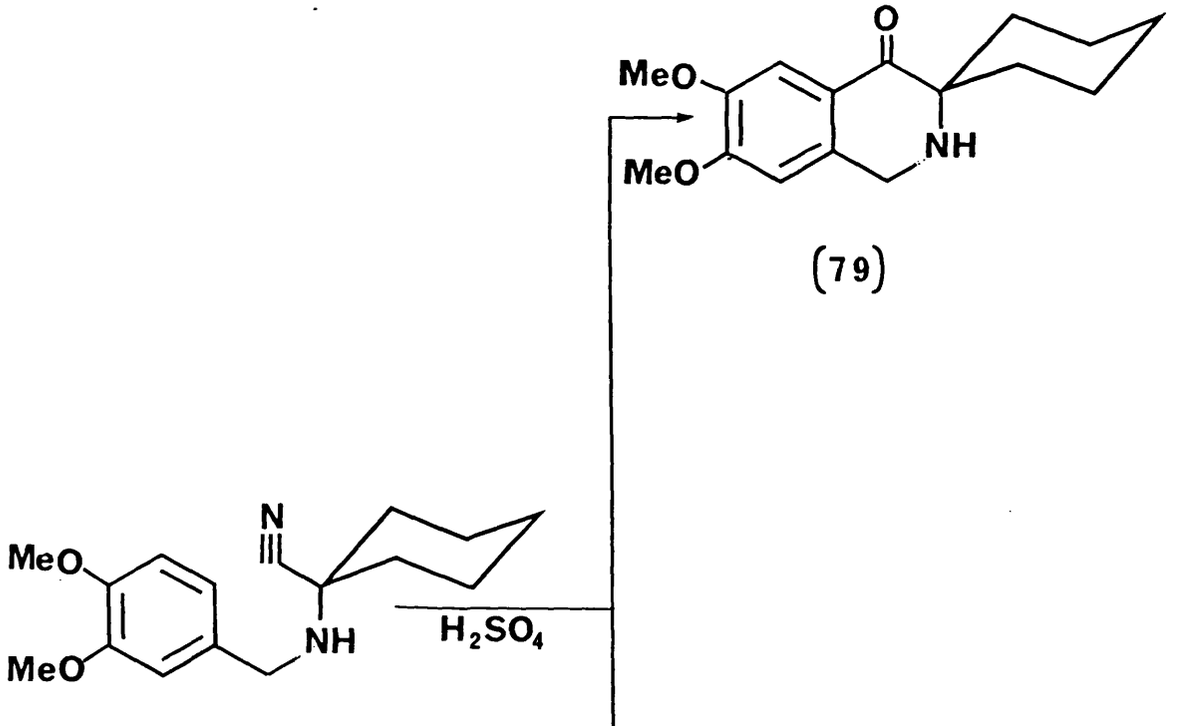
The spectroscopic data (tables 7 and 8) of these amino-nitriles were consistent with previously[51,88] assigned structures.

2.1.2 Cyclisation of 1-(3,4-dimethoxybenzylamino) cyclohexane carbonitrile (58)

Cyclisation of the 3,4-dimethoxybenzylaminonitrile (58) gave a single dialkoxyisoquinolinone whose spectroscopic data (tables 11 and 12 pages 183 and 189) and the melting point were in accord with those reported by Harcourt and Waigh[51] for 6,7-dimethoxyisoquinolinone (79). In addition to this dialkoxyisoquinolinone (79) a single phenolic component was obtained which was not isolated by Harcourt and Waigh[51], whose melting point and spectroscopic data (tables 11, 12 and 17, pages 183,189 and 199) were consistent with that for the 7-hydroxy-6-methoxyisoquinolinone[88] (80, obtained by Nasir from cyclisation of 4-ethoxy-3-methoxy-benzylaminoacetonitrile, 59).

The 6,7-dimethoxyisoquinolinone (79) is the major product when cyclisation is carried out at -10° and room temperature; but at 50° the ratio of dialkoxy to phenolic product is reversed, the former being obtained in only 15% yield. This is not in accord with the observations of Harcourt and Waigh[51].

Although the total recovery of products was fairly constant (80-85%), the ratio of dialkoxyisoquinoline and phenolic isoquinolinone depended upon the temperature of cyclisation (scheme 40).



(58)

(79)

(80)

Compd.	Yield (%) at -10°	R.T.	50°
79	75	60	15
80	10	21	65

Scheme 40

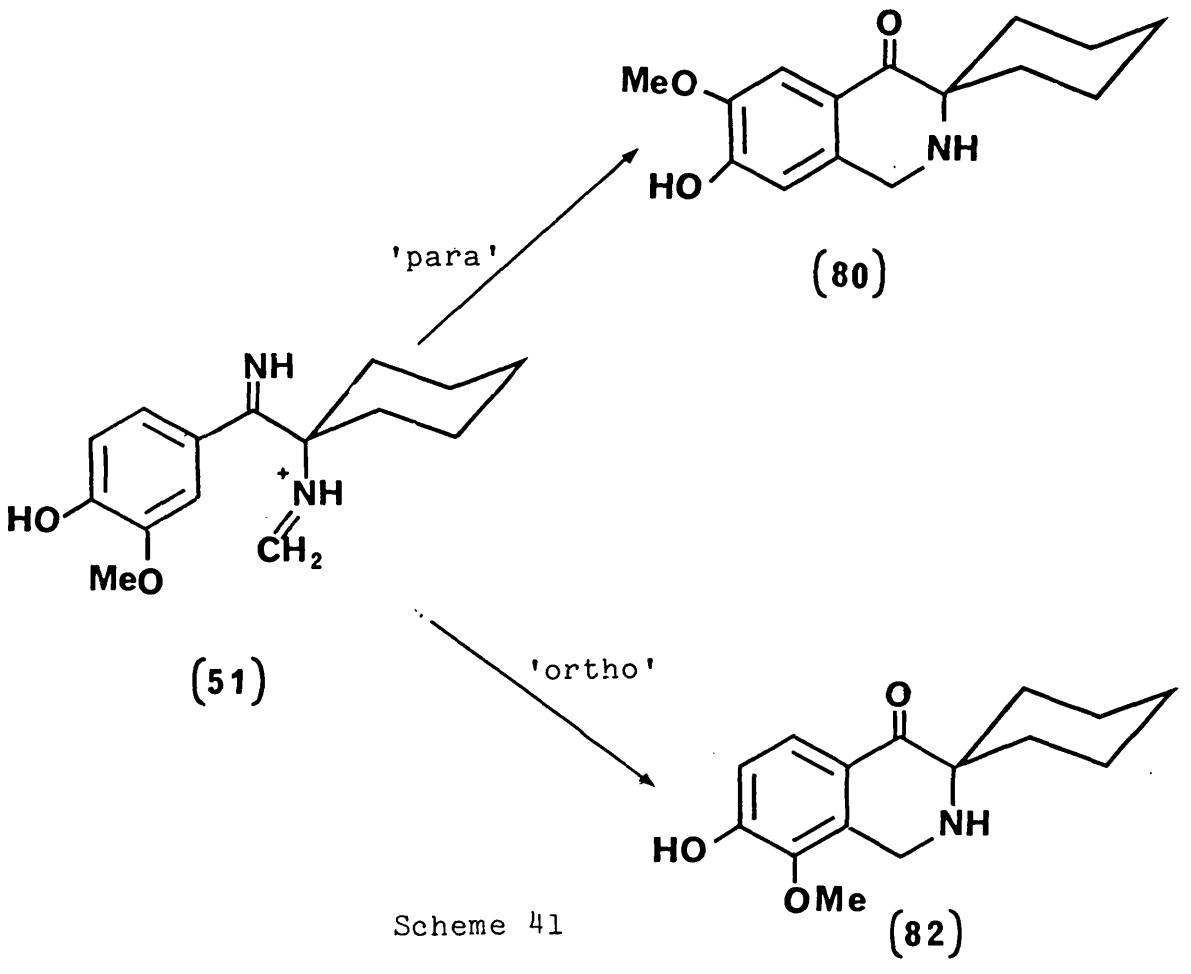
2.1.3 Cyclisation of 1-(4-ethoxy-3-methoxybenzylamino) cyclohexane carbonitrile (59)

Cyclisation of the aminonitrile (59, performed as above) gave a single dialkoxyisoquinolinone which had m.p. and spectroscopic data (tables 11 and 12, pages 183 and 189) identical to that reported by Nasir, for the 7-ethoxy-6-methoxyisoquinolinone (81).

The orientation of the dialkoxy substituents was established by preparing the 4-benzyl-4-hydroxytetrahydroisoquinoline (115). The data (tables 18-20, pages 202,205,210) are identical with those quoted by Nasir and assignment is totally unambiguous.

The crude phenolic product was shown by t.l.c. to consist of two components which were separated by a preparative t.l.c. The major component was identical in all respects to the 7-hydroxy-6-methoxyisoquinolinone reported by Nasir. The minor phenolic product had ^1H n.m.r. spectrum which showed two doublets (J = 8 Hz) at δ 7.60 ppm (1H) and 6.70 ppm (1H) and clearly is a 7,8-disubstituted isoquinolinone. On addition of NaOD in D_2O, the doublet at δ 6.70 ppm underwent an upfield shift to δ 6.15 ppm, showing that the phenolic hydroxyl substituent is at C7. This was confirmed by ultraviolet spectroscopy (table 17, page 199) which showed the phenolic group to be <u>para</u> to the C4 carbonyl function (82).

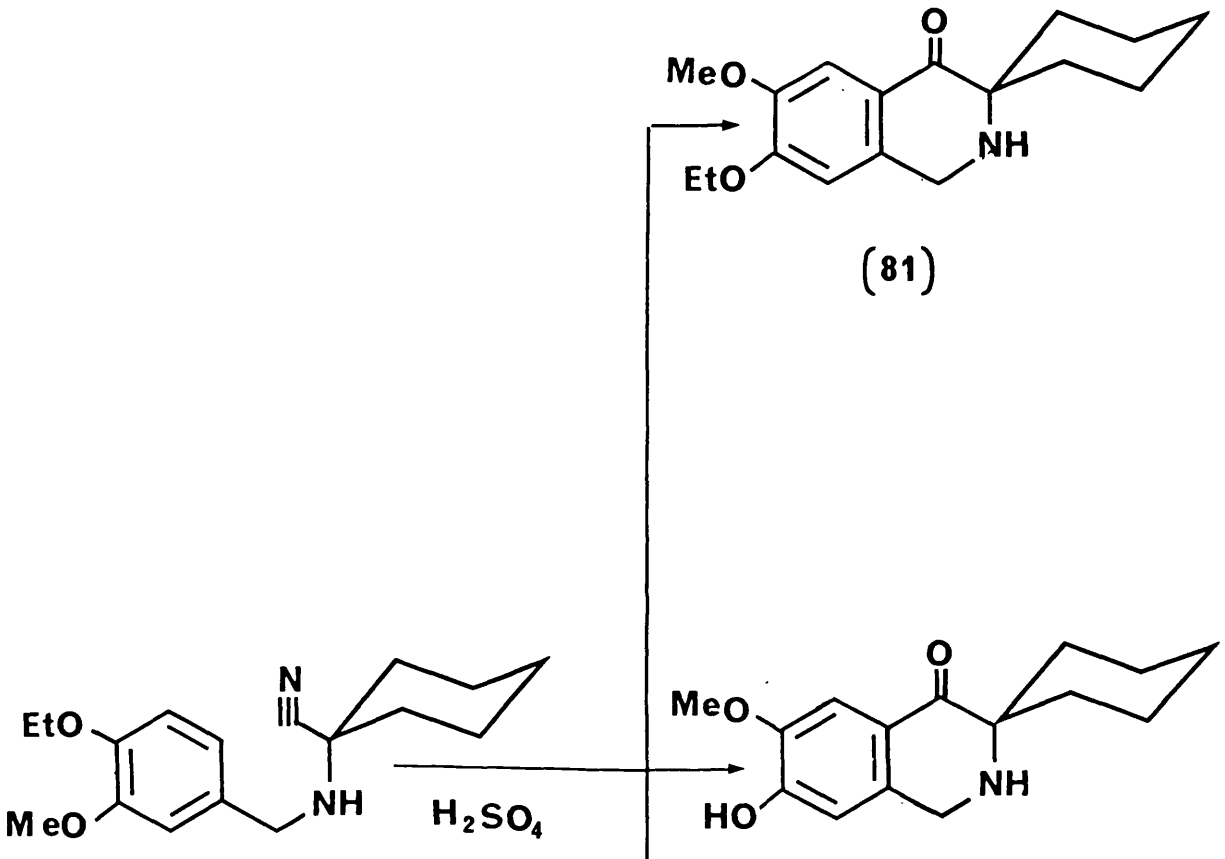
The presence of this product, hitherto unreported, suggests that an atypical Pictet-Spengler cyclisation of the iminium ion (51) <u>ortho</u> rather than <u>para</u> to the alkoxy substituent occurs (scheme 41).



Scheme 41

However, very low yields (max. 3.9%) indicate that this is not a particularly favourite course.

Apart from the presence of a second phenolic component, the major difference between these results and those reported by Nasir, is the isolation of the 7-hydroxy-6-methoxyisoquinolinone (80) in 22% yield (scheme 42) at room temperature. At -10^{o} the yield of this phenolic product is still significant (15%) which is probably an indication of the labile nature of the ethoxy group particularly when participating in the formation of the spiro-intermediate (see later section for a fuller discussion of the de-alkylation process).



Compd.	Yield (%) at -10°	R.T.	50°
81	72	52 (lit[88] 60)	2.6
80	15	22	65 (lit[88] 63)
82	3	3.3	2.2

Scheme 42

2.1.4 Cyclisation of 1-(3-ethoxy-4-methoxybenzylamino) cyclohexane carbonitrile (60)

Cyclisation of the aminonitrile (60, by the general method described above) at -10^{o} gave a dialkoxyisoquinolinone whose melting point and spectroscopic data (tables 11 and 12, pages, 183 and 189) were in accord with those reported by Nasir[88], for the 6-ethoxy-7-methoxyisoquinolinone (83). The orientation of the C6 and C7 substituents was again established by introducing the benzyl group at the C4 position. The data obtained (tables 18-20, pages 202 and 210) were consistent with those quoted by Nasir.

The phenolic product isolated at this temperature had a ^{1}H n.m.r. spectrum which exhibited two singlets at δ 7.25 (1H) and δ 6.30 ppm (1H) and the appearance of a quartet (δ 4.18-4.00 ppm) and triplet (δ1.29-1.25 ppm) characteristic for the ethoxyl group and clearly is an ethoxyhydroxyisoquinolinone (85).

The orientation of the C6 and C7-substituents was established by treatment with NaCD in D_2O, which resulted inasignificant shift to the higher field of the signal due to the C5-H (δ7.08 ppm) and C8-H (δ6.0 ppm), representing upfield shifts of 17 Hz and 30 Hz respectively, showing that the phenolic hydroxyl group is located at C7 (figure 7). These results were further confirmed by ultra-violet spectroscopic data (table 17, page199) and by preparing the 4-benzyl-4-hydroxytetrahydroisoquinoline (118, tables 18-20, pages, 202 and 210).

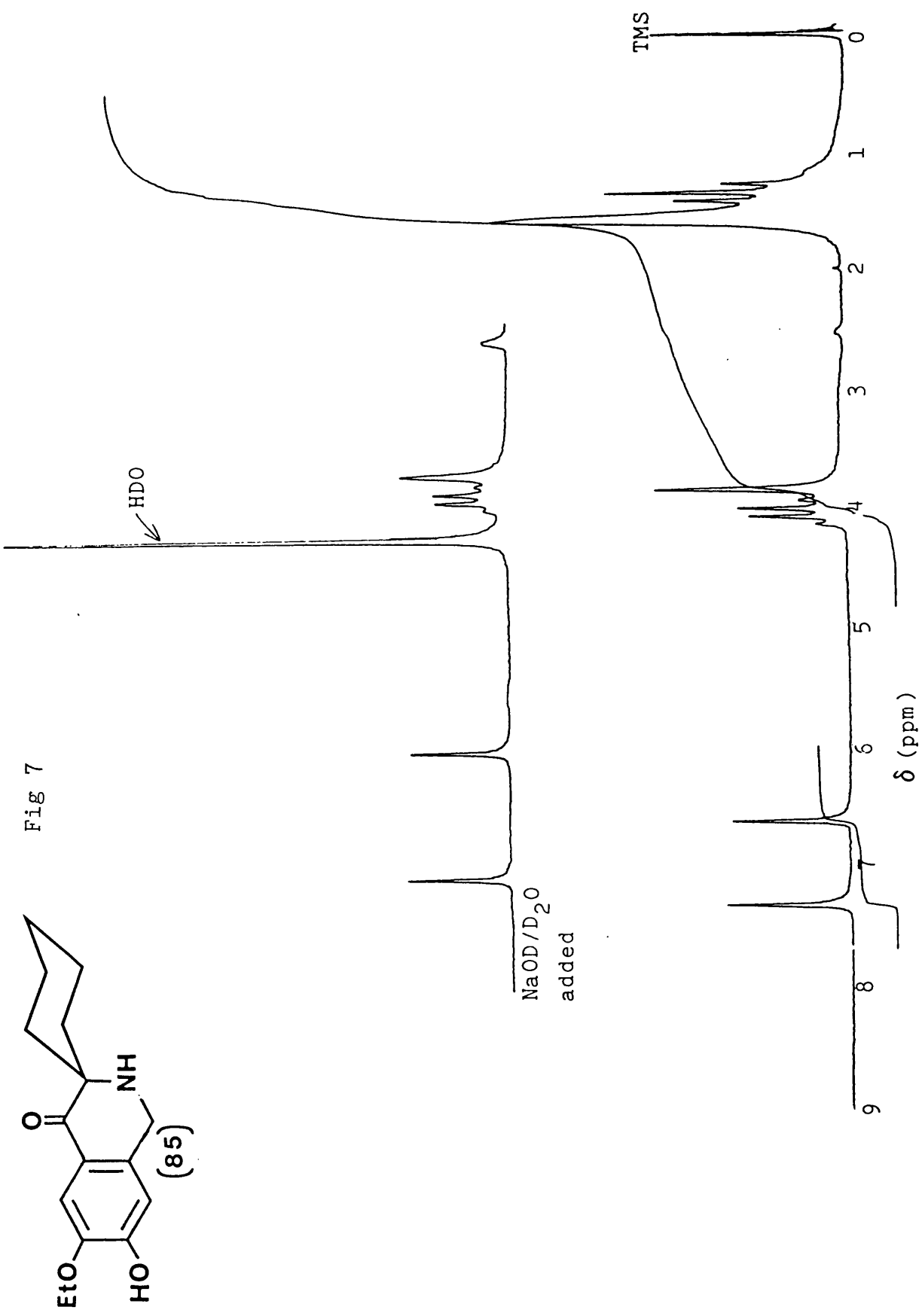


Fig 7

Cyclisation performed at room temperature gave one dialkoxy-product which was identical in all respects to the 6-ethoxy-7-methoxyisoquinolinone (83).

Chromatographic analysis (t.l.c.) of the crude phenolic product revealed two components which were separated by fractional recrystallisation using petroleum-ether (60-80°)/ ethylacetate (2:1).

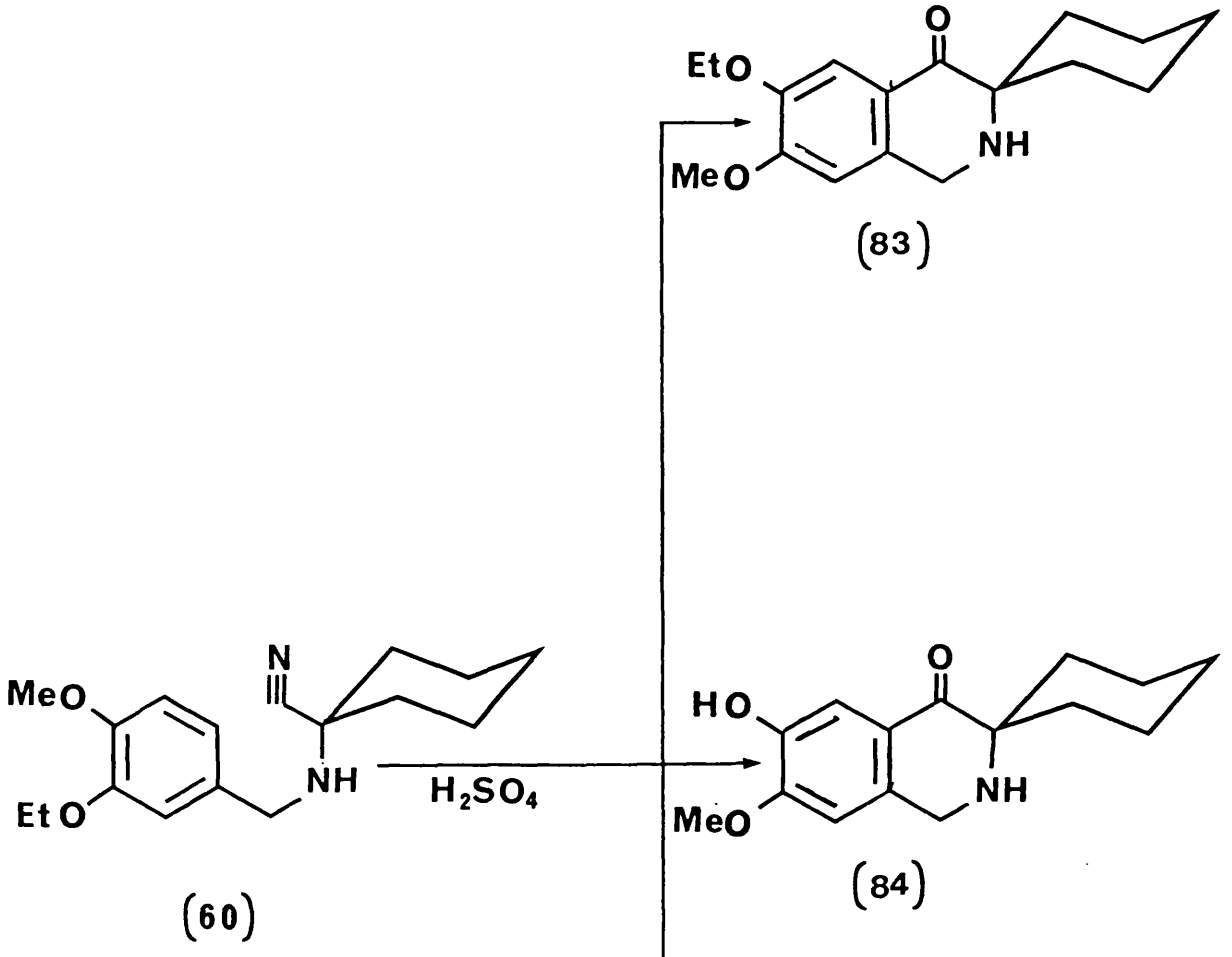
The major component, which was isolated in 35% yield, was the 6-ethoxy-7-hydroxyisoquinolinone (85). The minor phenolic product (obtained in 25% yield) had melting point and spectroscopic data (tables 11 and 12, pages 183 and 189) which were consistent with those reported by Nasir for the 6-hydroxy-7-methoxyisoquinolinone (84).

The orientation of hydroxy and methoxy substituents was established by ultra-violet spectroscopy (table 17, page 199) NaOD shift technique and by preparing a 4-benzyl derivative. the These results (obtained from cyclisation performed at room temperature) are in contrast to those reported by Nasir, who isolated the hydroxymethoxyisoquinolinone (84) as the sole phenolic product.

By comparison cyclisation carried out at 50° resulted in an 8% yield of dialkoxyisoquinolinone (again in contrast to the earlier report[88], where this product was not isolated) whose spectroscopic data (tables 11 and 12, pages 183 and 189) and the melting point were in accord with 6-ethoxy-7-methoxy-isoquinolinone (83).

Furthermore, only a single phenolic product was isolated at this temperature, which was identical in all respects

to the 6-hydroxy-7-methoxyisoquinolinone (84). The yields of these cyclised products again depended upon the temperature of the cyclisation (scheme 43).



Compd	Yield (%) at -10°	R.T.	50°
83	58	20 (lit[88] 20)	8 (lit[88] 0)
84	0	25 (lit[88] 24)	48 (lit[88] 44)
85	32	35	0

Scheme 43

The total recovery of product from the above three aminonitriles varies in yield, for example at 50° for :-

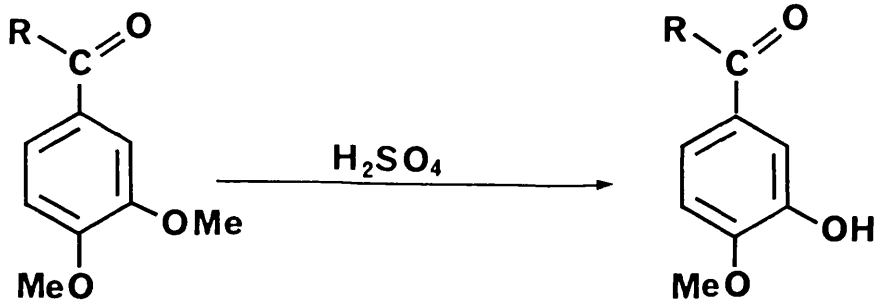
3,4-dimethoxyaminonitrile (58) this is	80%
4-ethoxy-3-methoxyaminonitrile (59)	70%
3-ethoxy-4-methoxyaminonitrile (60)	56%

The relatively low recovery of products from cyclisation of the amino nitrile (60), could well be a reflection of the lability of the ethoxy group (especially at the higher temperatures) resulting in the formation of the 6,7-dihydroxy-isoquinolinone, which under the conditions of extraction employed probably remained in the aqueous phase.

The above results are consistent with the involvement of the spirocyclic-intermediate. No products arising from the classical cyclisation were obtained.

2.2.0 O-Dealkylation of the alkoxy-groups

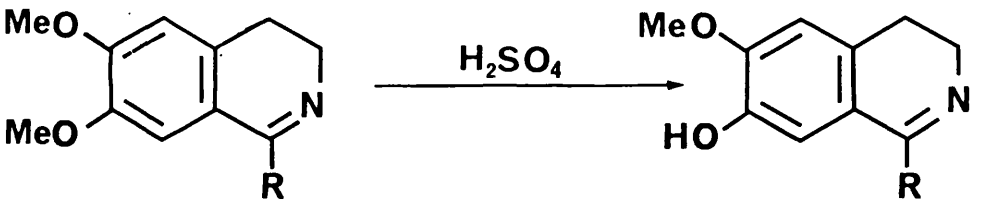
Brossi and co-workers[95] have described the selective O-demethylation of 3,4-dimethoxybenzaldehyde and the corresponding acetophenone in concentrated sulphuric acid at 65° to yield the 3-hydroxy-4-methoxy analogue.



R = H; 3,4-dimethoxybenzaldehyde

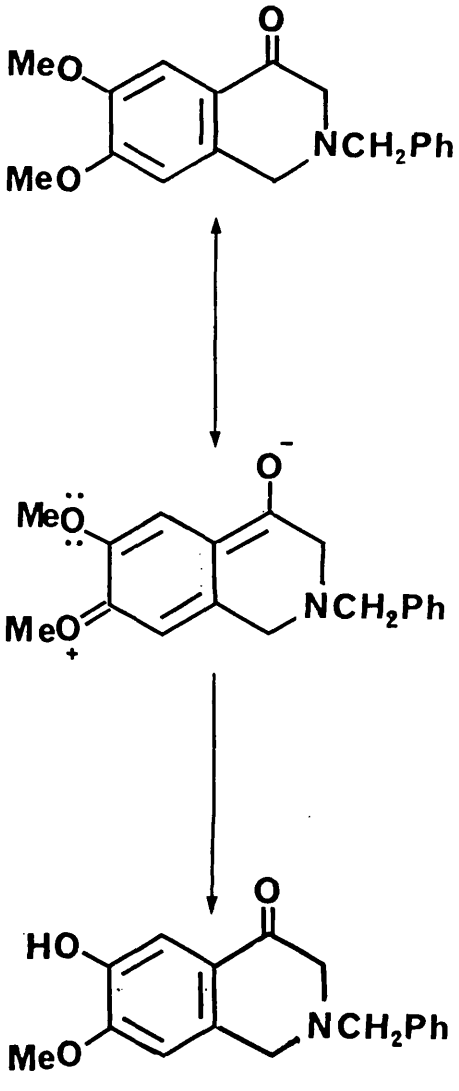
R = CH_3; 3,4-dimethoxyacetophenone

Similarly Bruderer and Brossi[96] have carried out the preferential O-demethylation of 6,7-dimethoxy-3,4-dihydroisoquinolinones under various acidic conditions (including concentrated sulphuric acid) to give 7-hydroxy-6-methoxy-3,4-dihydroisoquinolines.



In both cases selective demethylation was explained on the bases that preferential protonation of the methoxy group with the higher electron density occurs; that is, the alkoxy group which is not conjugated with the carbonyl or imino function.

Grethe and co-workers[91] had subsequently carried out selective demethylation of the C6-methoxyl group in the 6,7-dimethoxyisoquinolinones with 48% HBr and glacial acetic acid (1:1) to obtain 6-hydroxy-7-methoxyisoquinolinones. This is also explained on the basis of conjugation between the methoxyl group at C7 and the carbonyl group (scheme 44).

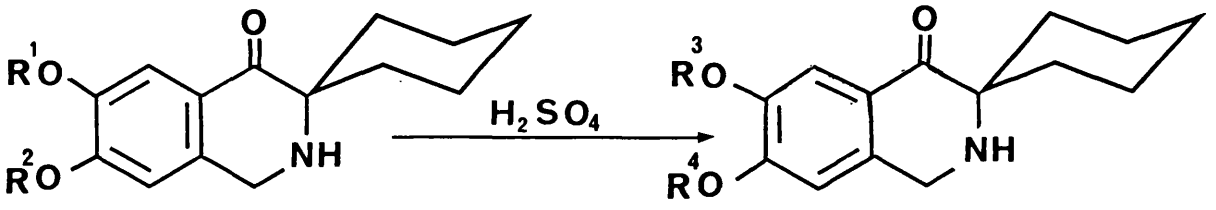


Scheme 44

Similarly, the dialkoxyisoquinolinones isolated from cyclisation of aminonitriles (58,59 and 60) were treated with concentrated sulphuric acid at -10°, room temperature and 50° to establish the pattern of O-dealkylation.

It was found that O-dealkylation was temperature dependent, hardly any dealkylation occurred at -10° except in the case of the 6-ethoxy-7-methoxyisoquinolinone (83), which presumably lost ethene to give the 6-hydroxy-7-methoxy-isoquinolinone (84) in 3% yield.

However, as the temperature for O-dealkylation was increased, so was the yield of phenolic products (scheme 45, see also table 21, page 215).

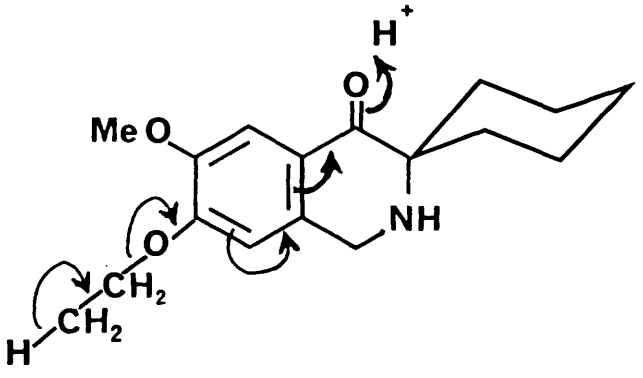


Dialkoxy isoquinolinone			Phenolic product obtained			Yield (%) at		
	R^1	R^2		R^3	R^4	-10°	R.T.	50°
79	Me	Me	84	H	Me	0	20	78
83	Et	Me	84	H	Me	3	36	85
81	Me	Et	80	Me	H	0	29	26

Scheme 45

Thus O-dealkylation of 6,7-dialkoxyisoquinolinones (79 and 83) both gave the 6-hydroxy-7-methoxyisoquinolinone (84). These are in accord with the observation of Grethe and co-workers[91].

However, O-dealkylation of the 7-ethoxy-6-methoxyisoquinolinone (81) is of particular interest. No de-alkylation was observed at -10° as is the general case, whereas at room temperature and 50° the 7-hydroxy-6-methoxyisoquinolinone is obtained. Thus, where the more labile ethoxy group is at C7, de-alkylation proceeds in a contrary manner to that observed by Grethe[91]. This again may be a reflection of the case with which ethene may be lost.



The low yield of phenolic product obtained at 50° in this instance is almost surely due to concomitant de-methylation yielding the 6,7-dihydroxyisoquinolinone, which, under the conditions of extraction employed, remained in the aqueous phase.

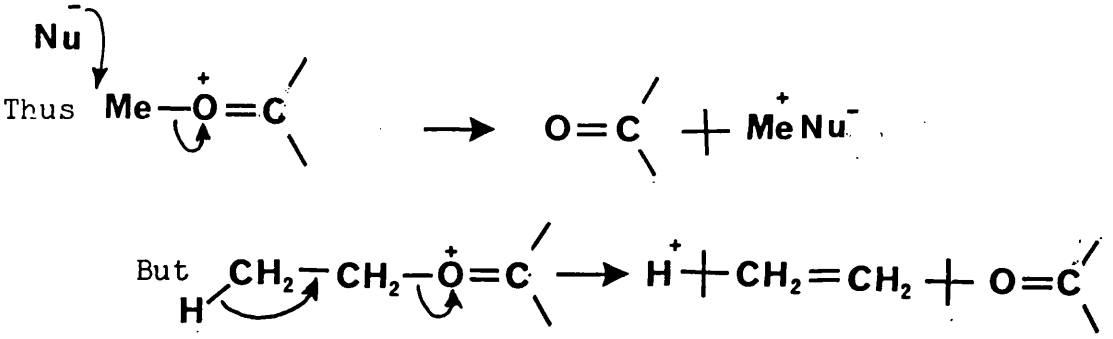
These results suggest that in concentrated (98%) sulphuric acid cyclisation does not proceed as far as the isoquinolinone stage. For example, in most cases selective O-dealkylation of the dialkoxyisoquinolinone at -10° did not yield any phenolic product, whereas cyclisation of benzylaminonitriles at this temperature resulted in significant amounts of phenolic product, especially when an ethoxy substituent was located at C4.

These observations suggest that in cyclisation of the aminonitriles O-dealkylation probably takes place at the spiro-intermediate stage.

Phenolic isoquinolinones from cyclisation of the amino-nitriles

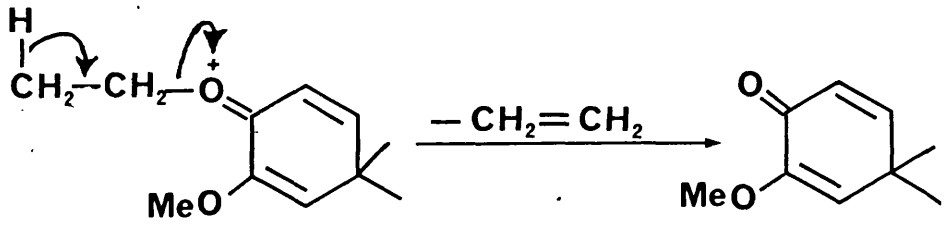
The formation of phenolic isoquinolinones from cyclisation of aminonitriles is the result of O-demethylation or O-de-ethylation which may occur via different mechanisms.

The loss of the methyl group requires an attack by a nucleophile, whereas the loss of ethyl group can be achieved by an additional mechanism involving elimination of ethene.



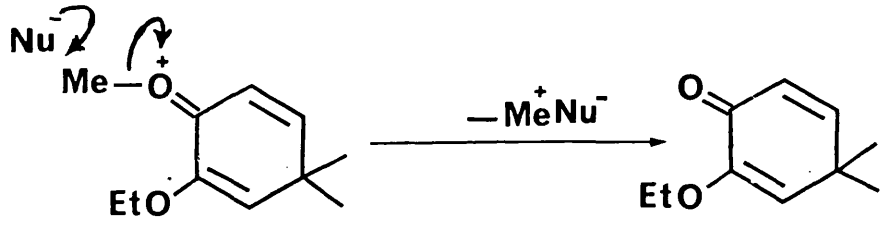
Vanillin Series

In the Vanillin Series, the phenolic product is hydroxymethoxy, this is because dealkylation is most likely to occur at the spiro-intermediate stage, and is probably easier for de-ethylation than demethylation.



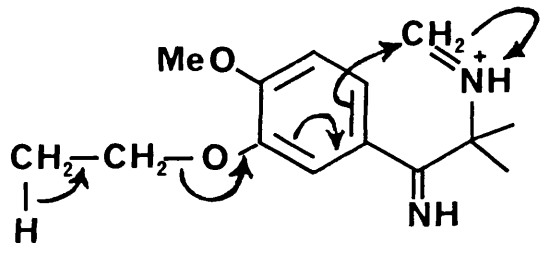
Isovanillin Series

In this series cyclisation at -10° resulted in an ethoxyhydroxy phenolic product, which is the result of O-demethylation occurring at the spiro-intermediate.



However, at room temperature and at 50°, the hydroxy-methoxyisoquinolinone is also produced. This reflects the

lability of the ethoxy group at higher temperatures. It is possible that at these temperatures O-de-ethylation occurs before the formation of the spiro-intermediate, although its elimination at a subsequent stage cannot be excluded.



2.3.0 Preparation and cyclisation of trideutero-methoxybenzylaminonitriles

Although cyclisation of the isomeric ethoxymethoxy-benzylaminonitriles has provided evidence for the exclusive formation of a spirocyclic intermediate. Cyclisation of simple 3,4-dimethoxybenzylaminonitriles had yet to be resolved. The closest system to this that could be approached, was cyclisation of the isomeric trideutero-methoxybenzylaminonitriles (65 and 66).

2.3.1 Preparation of 1-(4-trideuteromethoxy-3-methoxy-benzylamino) cyclohexane carbonitrile (65) and 1-(3-trideuteromethoxy-4-methoxybenzylamino) cyclohexane carbonitrile (66)

The trideuteromethoxybenzylaminoacetonitriles were prepared by the general route from the appropriate trideuteromethoxybenzaldehyde (which were prepared from vanillin and isovanillin respectively by the procedure described by Vyash and Shah[97] with slight modification).

The spectroscopic data (tables 7 and 8, pages 167 and 170) of these aminonitriles were unambiguous.

2.3.2 Cyclisation of 1-(4-trideuteromethoxy-3-methoxy-benzylamino) cyclohexane carbonitrile (65)

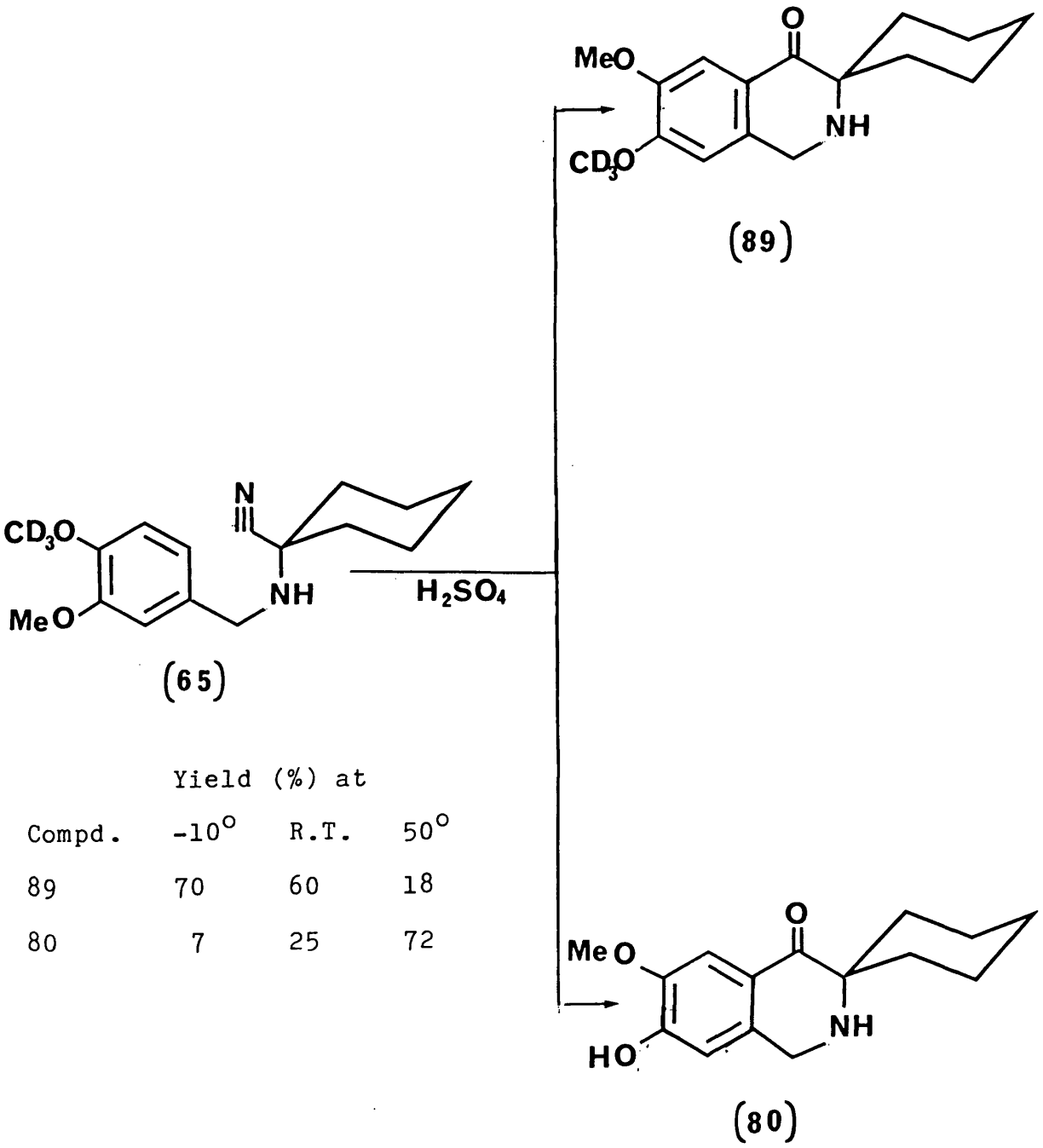
The general method of cyclisation (section 2.0.2, page 49) was again employed.

The yields of dialkoxy - and phenolic isoquinolinone obtained at -10°, closely paralleled those obtained in the cyclisation of the dimethoxy-nitrile (58, scheme 40, page 64).

The phenolic product that was obtained showed the presence of a methoxy group in its ^{1}H n.m.r. spectrum, and was identical in all respects (including ^{1}H n.m.r.-NaOD and ultra-violet shift data) to the previously characterised 7-hydroxy-6-methoxyisoquinolinone (80).

The dialkoxyisoquinolinone was treated with concentrated sulphuric acid, as for the dimethoxy counterpart described in the previous section. At 50° a phenolic product was obtained in 80% yield which showed the absence of a methoxy group in its ^{1}H n.m.r. spectrum. The ^{1}H n.m.r.-NaOD shift data and ultra-violet spectroscopic data (table 17, page 200) confirmed that the hydroxy group was located at C6. In view of the selective O-demethylation at C6 observed for the 6,7-dimethoxyisoquinolinone (79), the product is the 7-trideuteromethoxy-6-hydroxyisoquinolinone (134, table 21, page 215), derived from the 7-trideuteromethoxy-6-methoxy-isoquinolinone (89).

The results obtained from this cyclisation are summarised in scheme 46.



Compd.	Yield (%) at -10°	R.T.	50°
89	70	60	18
80	7	25	72

Scheme 46

2.3.3 Cyclisation of 1-(3-trideuteromethoxy-4-methoxy-benzylamino) cyclohexane carbonitrile (66)

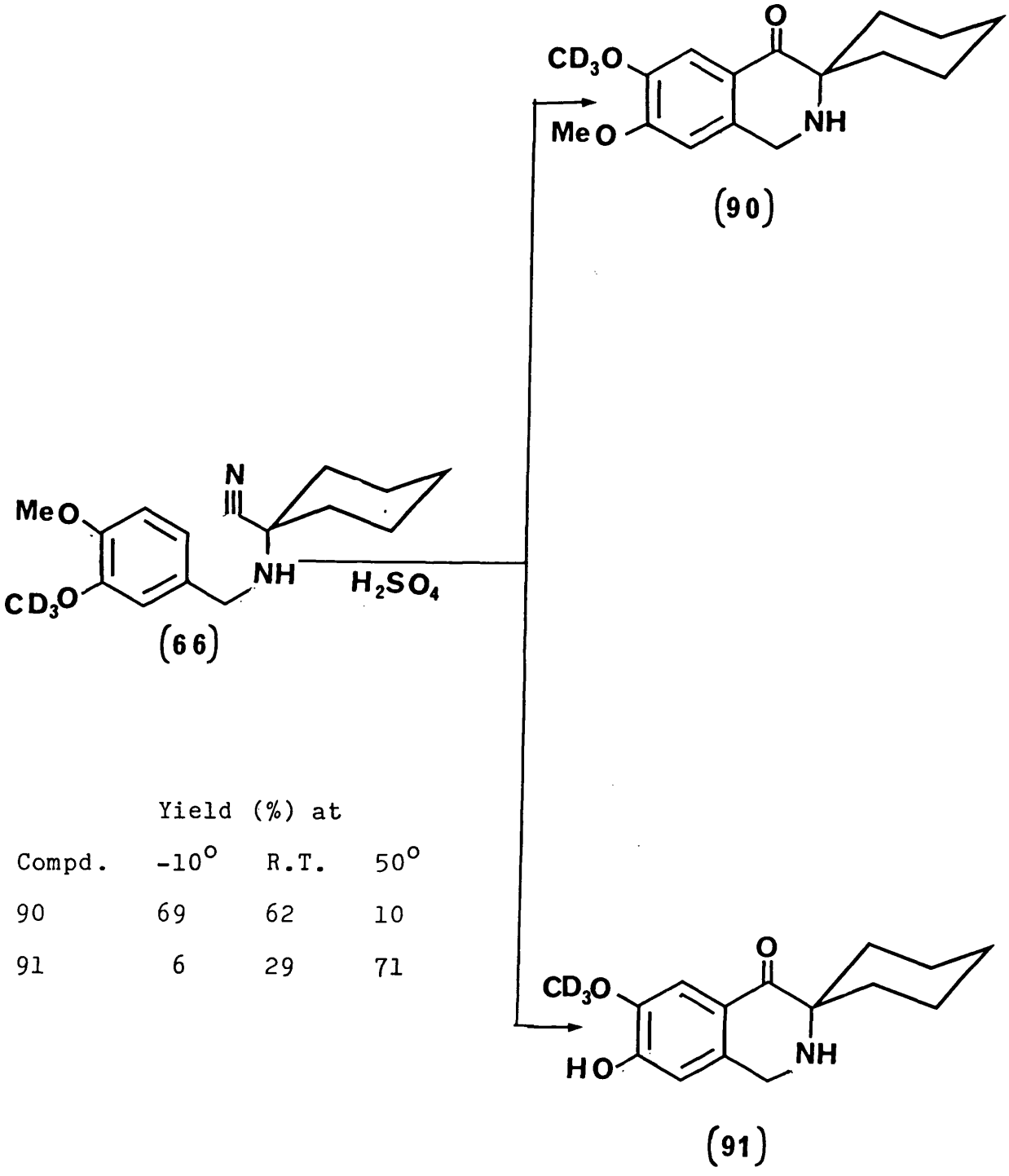
Cyclisation of the benzylaminonitrile with the reverse order of dialkoxy substituents (66) gave a phenolic product (91), the ^{1}H n.m.r. spectrum of which showed the absence of a methoxy group. The orientation of the hydroxy group was established by the NaOD shift technique which produced an upfield shift of 22 Hz and 60 Hz for the signals due to the C5 and C8 protons respectively. The hydroxy group is therefore at C7, which was confirmed by ultra-violet data which clearly showed conjugation of the phenolic substituent with the carbonyl group.

The dialkoxyisoquinolinone was subjected to selective O-dealkylation using sulphuric acid, and gave the previously characterised[88], 6-hydroxy-7-methoxyisoquinolinone (84). Thus the dialkoxyisoquinolinone has the 6-trideuteromethoxy--7-methoxy orientation of alkoxy substituents (90).

Yields for products isolated under different temperature conditions are given in scheme 47.

In contrast to the ethoxymethoxybenzylaminonitriles, cyclisation of the two isomeric deuterium labelled dimethoxybenzylaminonitriles gave approximately the same ratio of dialkoxy to phenolic isoquinolinone irrespective of the orientation of the alkoxy groups.

Again, the results are entirely in accord with involvement of the spirocylic intermediate. No evidence of classical cyclisation was found.



Compd.	Yield (%) at -10°	R.T.	50°
90	69	62	10
91	6	29	71

Scheme 47

2.4.0 Preparation and cyclisations of alkoxyhydroxy-benzylaminoacetonitriles

Cyclisations of the isomeric ethoxymethoxybenzylamino-acetonitriles have been shown to proceed exclusively via the spirocyclic intermediate.

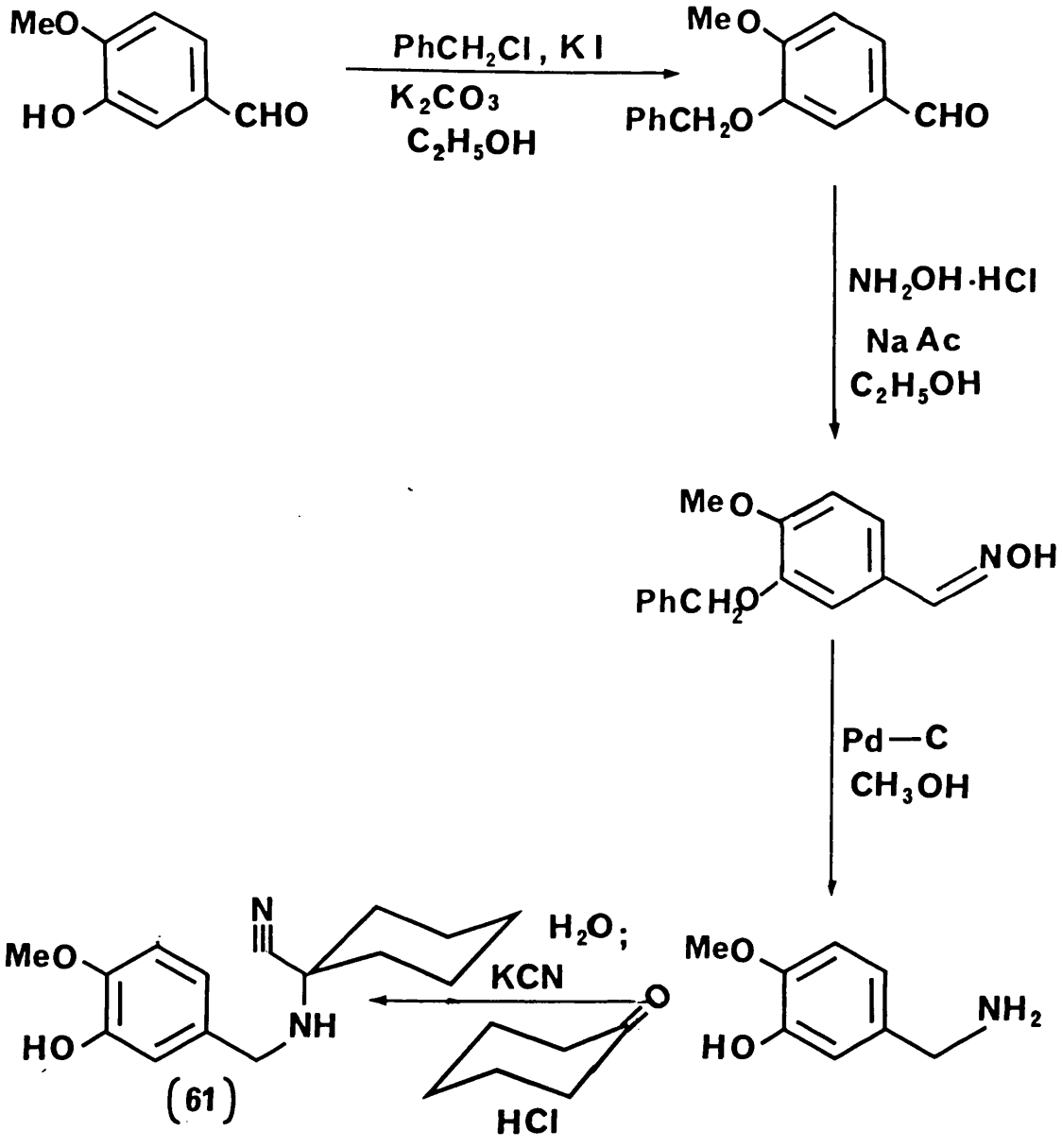
If this is indeed the pathway, then it could be expected that cyclisation of the alkoxyhydroxy analogues would give alkoxyhydroxyisoquinolinones with the same orientation as that which obtained in the cyclisation of the isomeric ethoxymethoxy aminonitriles.

This approach has been undertaken in the present investigation to provide further evidence for the involvement of the spiro-intermediate and to gain a clearer picture of the effect of temperature on the process of O-dealkylation.

2.4.1 Preparation of 1-(4-hydroxy-3-methoxybenzylamino) cyclohexane carbonitrile (61) and 1-(3-hydroxy-4--methoxybenzylamino) cyclohexane carbonitrile (62)

The hydroxymethoxybenzylaminoacetonitriles (61 and 62) were prepared from vanillin and isovanillin respectively by a standard procedure (scheme 48). For example, vanillin was benzylated (using the modified method of Geissman and Moje[98]) and converted to the oxime. Catalytic reduction by means of hydrogen and palladium brought about debenzylation and reduction of the oxime to the amine. The amine was then used without further purification in the Strecker synthesis to produce the aminonitrile (61). Both aminonitriles gave

virtually identical spectroscopic data (tables 7 and 8, pages 166 and 170), which differed in their ^{1}H n.m.r spectra from the dimethoxy analogue (58) by the presence of only one methoxy signal (δ3.7 ppm).



Scheme 48

2.4.2 Preparation of 1-(3-ethoxy-4-hydroxybenzylamino) cyclohexane carbonitrile (63) and 1-(4-ethoxy-3--methoxybenzylamino) cyclohexane carbonitrile (64)

The ethoxyhydroxybenzylaminoacetonitriles (63 and 64) were prepared from appropriate ethoxyhydroxybenzaldehyde by the procedure outlined in scheme 48.

^{1}H n.m.r. data (table 7, page 166), these aminonitriles were similar to their corresponding methoxyhydroxy analogues, except for the signal due to the alkoxy groups.

2.4.3 Cyclisation of 1-(4-hydroxy-3-methoxybenzylamino) cyclohexane carbonitrile (61) and 1-(3-hydroxy-4--methoxybenzylamino) cyclohexane carbonitrile (62)

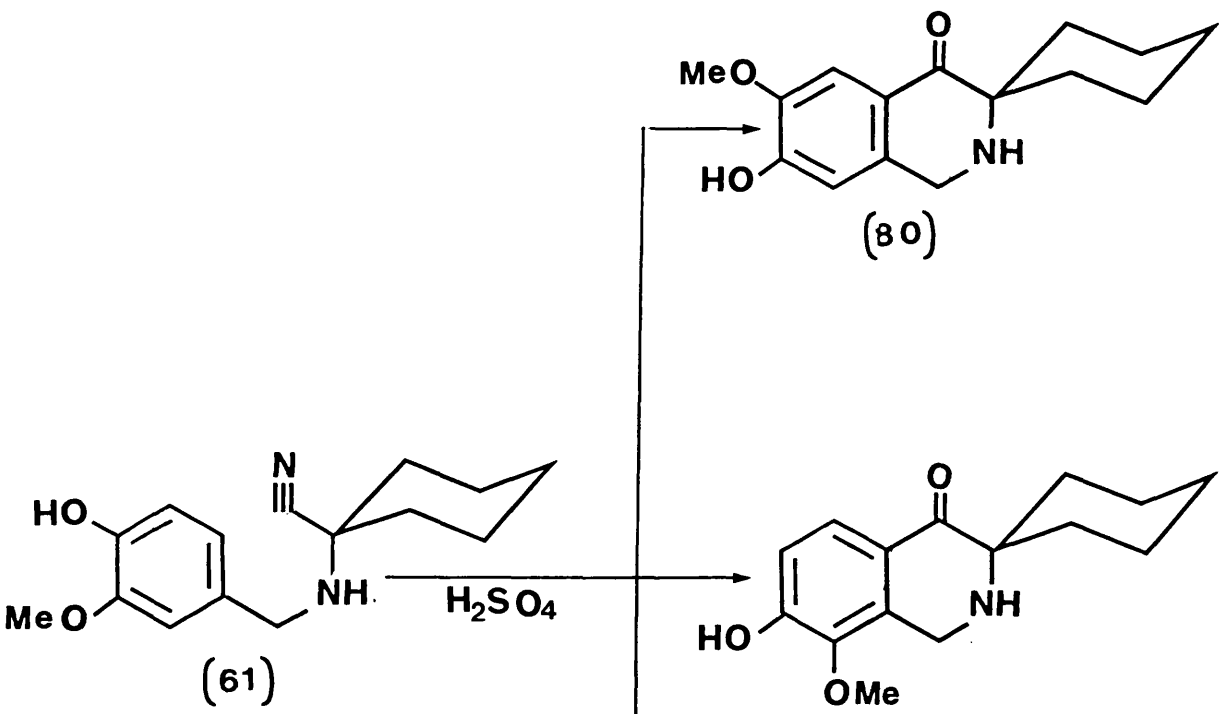
Cyclisation of the alkoxyhydroxybenzylaminoacetonitriles (61 and 62) and isolation of crude products were performed under identical conditions as to the previous cyclisations; except that the crude phenolic products were obtained by continuous extraction with chloroform for 24 hours.

Chromatographic (tlc) analysis of the crude products showed a mixture of phenolic products, which were separated by column chromatography.

Thus under all three conditions of cyclisation, the aminonitrile (61) gave 7-hydroxy-6-methoxyisoquinolinone (80), as the major product. Two minor products, namely the 7-hydroxy-8-methoxyisoquinolinone (82) and 6,7-dihydroxy-isoquinolinone (86) were obtained. There were only minor variations in yield with respect to variation of temperature (scheme 49).

The major phenolic product (80) and the minor component (82) had melting points and spectroscopic data (tables 11 and 12, pages 183 and 189) which were consistent with those phenolic products obtained from the 4-ethoxy-3-methoxy-benzylaminonitrile (59). The orientation of the hydroxyl group in these products were also established by means of the NaOD shift (table 11, page 183) and ultra-violet spectroscopy (table 17, page 199).

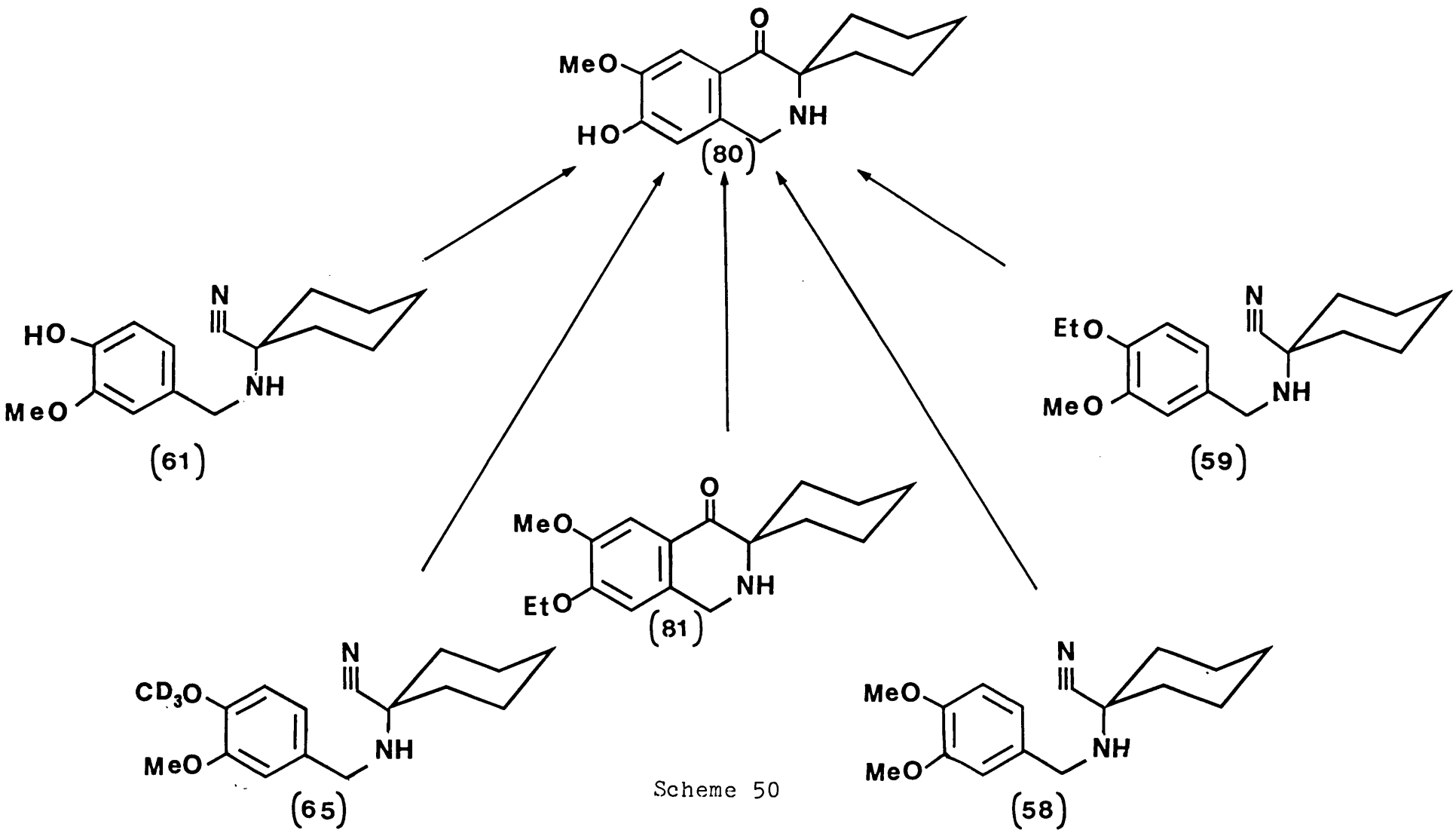
The formation of the 7-hydroxy-6-methoxyisoquinolinone (80) via different reaction sequences is illustrated in scheme 50.



Compd.	Yield (%) at -10°	R.T.	50°
80	86	80	70
82	4	3.9	3.0
86	3	4	7

Scheme 49

2,3-dihydro-7-hydroxy-6-methoxyisoquinolin-4(1H)-one-3-spirocyclohexane



Scheme 50

By analogy cyclisation of the 3-hydroxy-4-methoxybenzyl-aminonitrile (62) gave one major component and two minor components. The major product had melting point and spectroscopic data identical to those of 6-hydroxy-7-methoxyisoquinolinone (84). Furthermore, the orientation of hydroxymethoxy substituents were confirmed by ultra-violet spectroscopy and the NaOD shift technique. The formation of this phenolic product from different reaction sequences is illustrated in scheme 52.

The ^{1}H n.m.r. spectrum (table 11, page 184) of the least minor component, namely 8-hydroxy-7-methoxyisoquinolinone (87) exhibited two doublets J = 8 Hz centred at 7.4 ppm (1H) and 6.3 ppm (1H) due to C5-H and C6-H respectively. On addition of 2-3 drops of NaOD in D_2O, no significant change in the spectrum was observed, confirming the location of the phenolic hydroxyl group at C8.

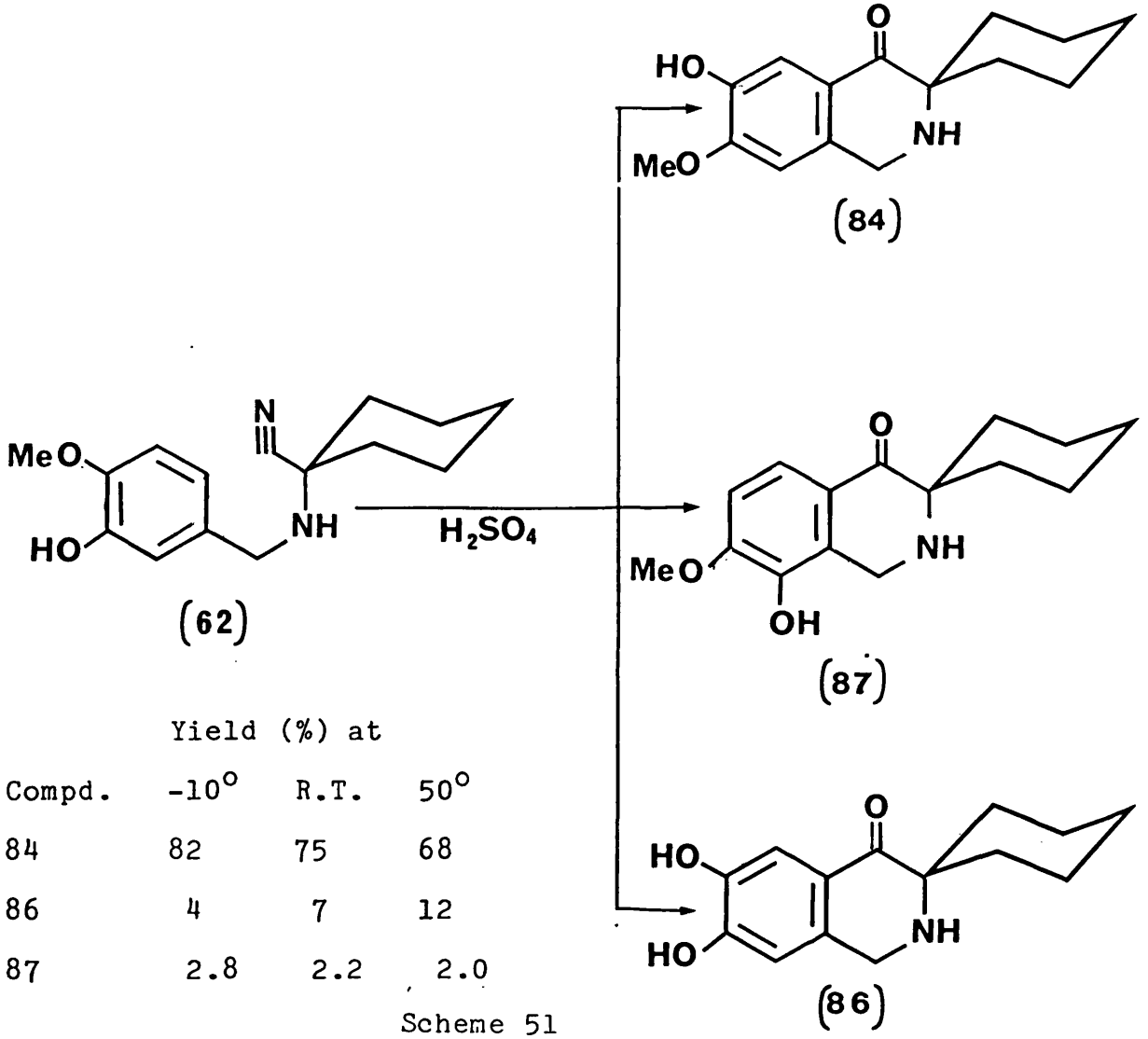
The third component was identical in all respects to dihydroxyisoquinolinone (obtained by cyclisation of the isomeric hydroxymethoxybenzylaminonitrile (61).

Again the yields of these product depended upon the temperature at which cyclisation was effected (scheme 51).

The dihydroxyisoquinolinone (86) obtained from cyclisation of aminonitriles (62) was in higher yields than from aminonitrile (61). It may be that in aminonitrile (62), the participation of the C4-methoxy group, in forming the spiro-intermediate increases its lability and hence resulting in higher yield of dihydroxyisoquinolinone (86) as compared to the cyclisation of aminonitrile (61), where the methoxyl group is at C3 and therefore, cannot participate in the formation of the spirocyclic-intermediate.

The most characteristic feature of the ^1H n.m.r. (table 11, page 184) of the dihydroxyisoquinolinone (86) was the appearance of two aromatic singlets at δ7.28 and 6.56 ppm, which upon treatment with NaOD were shifted to higher field (δ6.60 and 5.88 ppm respectively) both representing a shift of 68 Hz.

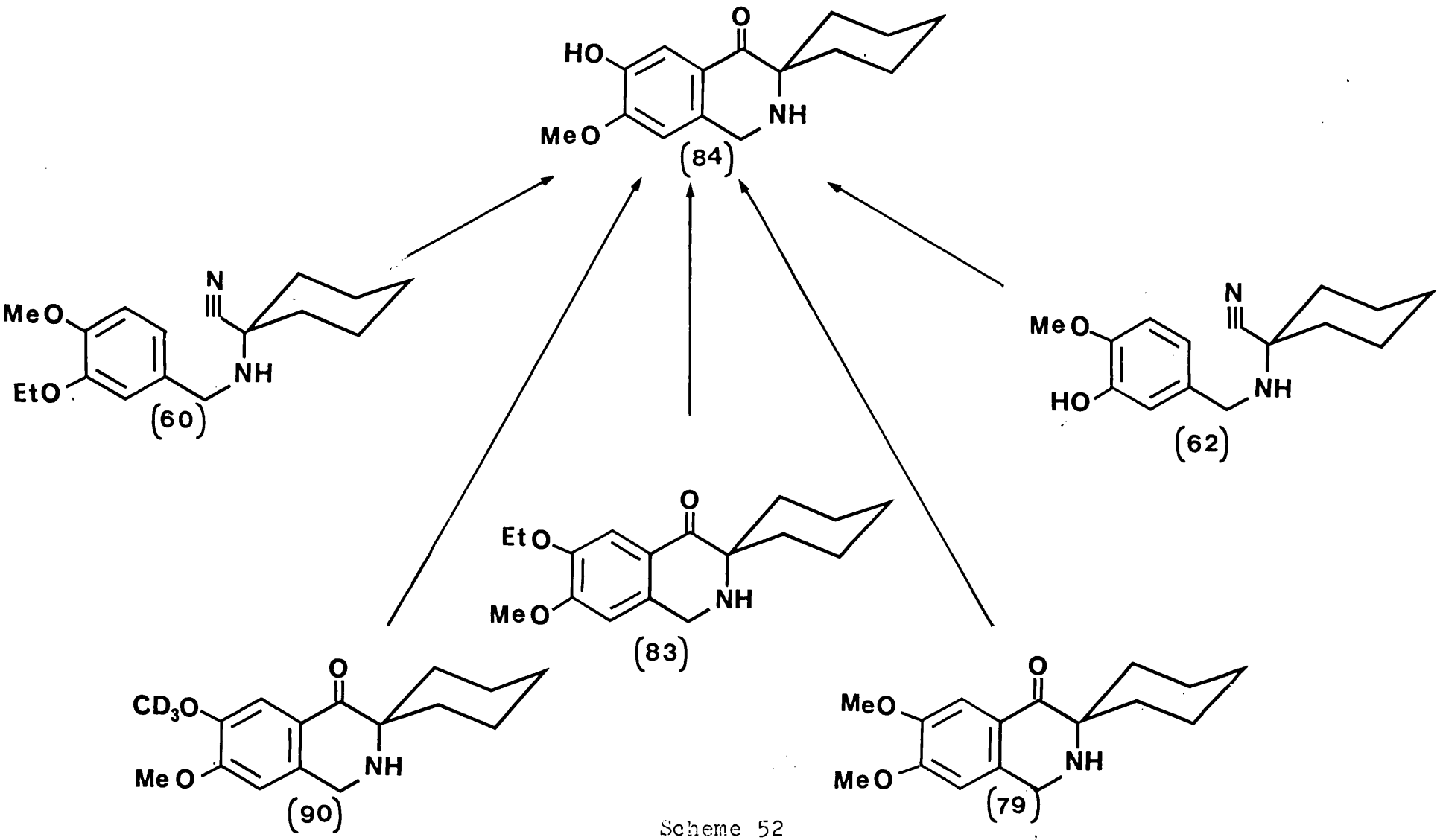
The electron impact mass spectrometry (table 12, page 190) showed the molecular ion (M^+) at m/z 247 (low eV), a peak at m/z 219 (70 eV) due to the loss of carbon monoxide, and base peak at m/z 123 (due to hydroxybenzyl cation, which presumably rearranges to tropylium ion). The retro Diels-Alder reaction of the molecular ion gave rise to a peak at m/z 150.



Compd.	Yield (%) at -10°	R.T.	50°
84	82	75	68
86	4	7	12
87	2.8	2.2	2.0

Scheme 51

2,3-dihydro-6-hydroxy-7-methoxyisoquinlin-4(1H)-one-3-spirocyclohexane



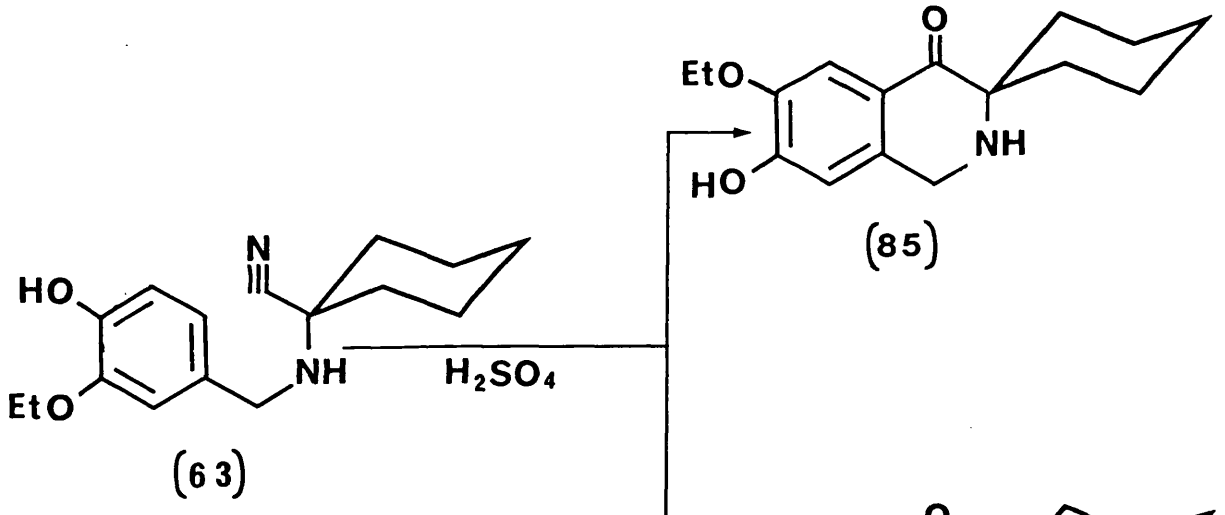
Scheme 52

2.4.4 Cyclisation of 1-(3-ethoxy-4-hydroxybenzylamino) cyclohexane carbonitrile (63) and 1-(4-ethoxy-3--methoxybenzylamino) cyclohexane carbonitrile (64)

Cyclisation of aminonitrile (63) performed under identical conditions to previous work gave a single ethoxy-hydroxyisoquinolinone which had m.p. and spectroscopic data (tables 11 and 12, pages 184 and 189) identical to the 6-ethoxy-7-hydroxyisoquinolinone (85), obtained from cyclisation (at -10^{o}) of the 3-ethoxy-4-methoxybenzylamino-acetonitrile (60). Accompanied by this was the minor component, which had melting point and spectroscopic data identical to the 6,7-dihydroxyisoquinolinone (86).

However, the products resulting from the ortho Pictet-Spengler cyclisation of iminium ion were not obtained.

The yields of these products (85 and 86) obtained from cyclisation of aminonitrile (63) are summarised in scheme 53.



Compound	Yield (%) at -10^{o}	R.T.	50^{o}
85	70	55	5
86	5	10	18

Scheme 53

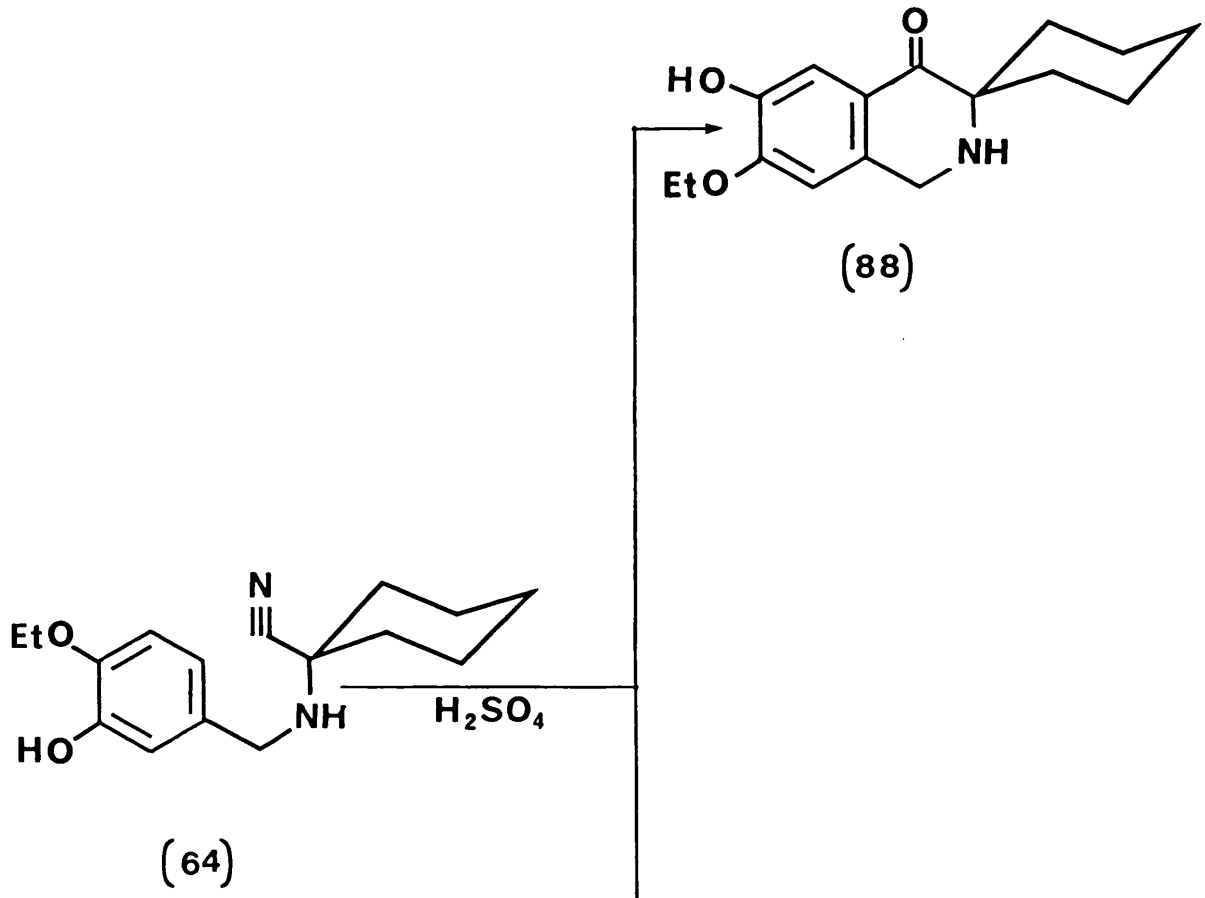
By comparison cyclisation of the isomeric aminonitrile (64) under identical conditions gave the major product, namely 7-ethoxy-6-hydroxyisoquinolinone (88) under all temperatures of the cyclisation.

Apart from the orientation of the hydroxyl group, the ^1H.n.m.r. spectrum of this product was similar to the 6-ethoxy-7-hydroxyisoquinolinone (85) isomer.

The orientation of C6 and C7 substituent in 7-ethoxy--6-hydroxyisoquinolinone (88) was established by the NaOD shift technique (table 11, page 184) and ultra-violet spectroscopy (table 17, page 199). Thus upon treatment with 2-3 drops of NaOD in D_2O the signals due to the C5 and C8 protons are shifted to higher field, representing a shift of 24 Hz and 17 Hz respectively and therefore confirming the location of the phenolic hydroxyl group at C6.

The minor product had melting and spectroscopic data which were consistent with that of the 6,7-dihydroxyisoquinolinone (86). Again the product(s) resulting from the ortho cyclisation were not obtained.

The yields of products (86 and 88) at different temperatures of cyclisation are summarised in scheme 54.



Compound	Yield (%) at -10°	R.T.	50°
88	60	34	3.2
86	8	14	29

Scheme 54

The yields of the dihydroxyisoquinolinone (86) obtained from cyclisation of ethoxyhydroxybenzylaminoacetonitriles (63 and 64) are higher than those obtained from cyclisation of hydroxymethoxy analogues (61 and 62). This is probably due to the greater lability of the ethoxy group as compared to the methoxy group[99].

The formation of the dihydroxyisoquinolinone (86) from different aminonitriles is summarised in scheme 55.

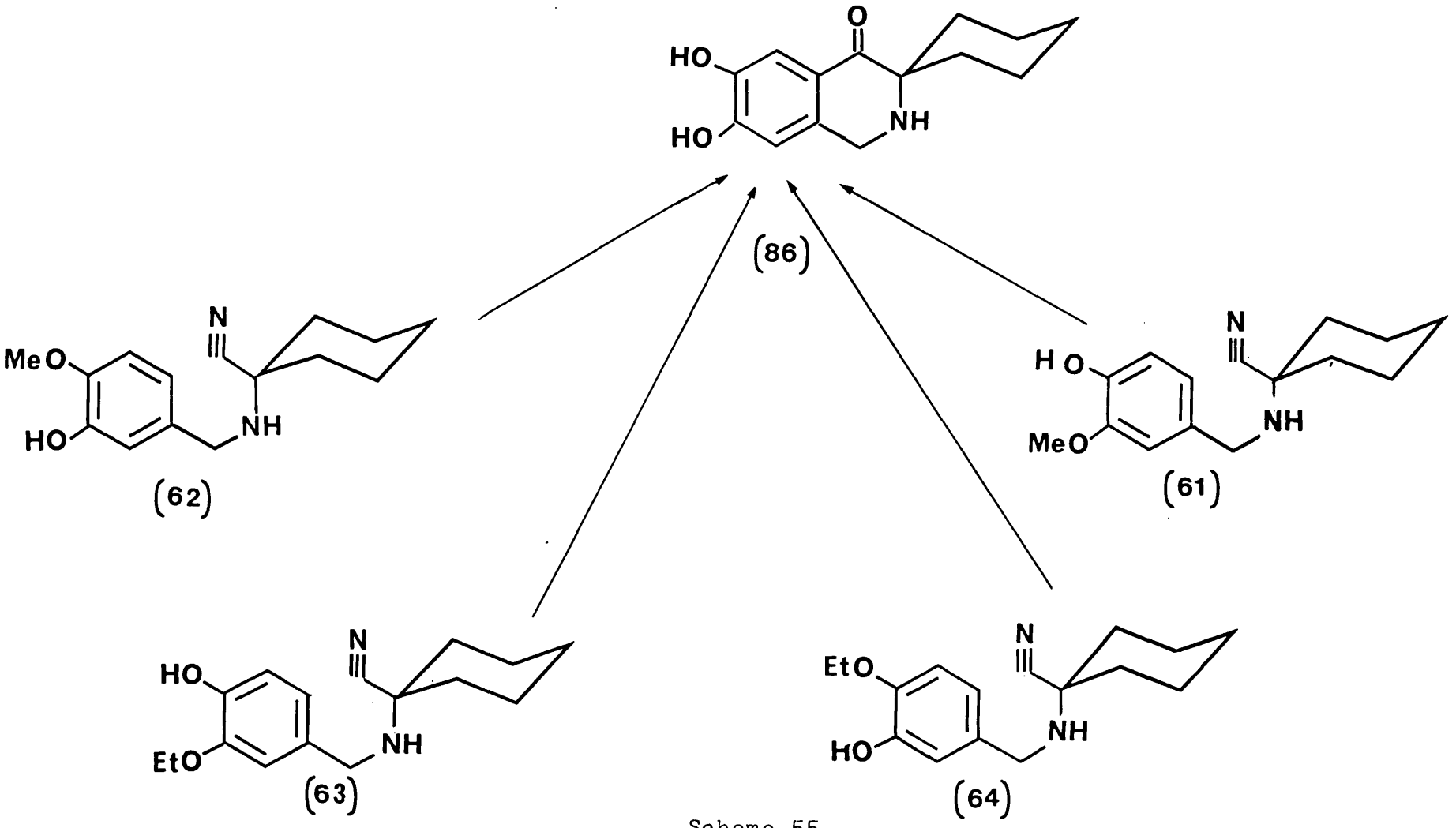
Cyclisation of the two isomeric hydroxymethoxyaminonitriles (61 and 62) gave approximately the same total recovery at each temperature. Furthermore only a minor variation in yields of the products was observed, with respect to the temperature.

However, significant difference in yields (relating to the temperature) was observed when the two isomeric ethoxyhydroxyaminonitriles (63 and 64) were cyclised.

This is probably due to the greater stability of the methoxy substituent (even at the spiro-intermediate stage, where O-dealkylation is likely to occur) as compared to the ethoxyl group, which is temperature labile.

The results are obtained from cyclisation of these ethoxyhydroxybenzylaminonitriles is a reflection of the lability of the ethoxy substituent (especially at 50^{o}). Furthermore the results indicate that O-de-ethylation is greatly favoured when the ethoxy group is <u>para</u> to the initial point of ring closure (ie. formation of spiro-intermediate). At this stage the ethoxyl group bears a positive charge which is a favourable situation to lose ethene.

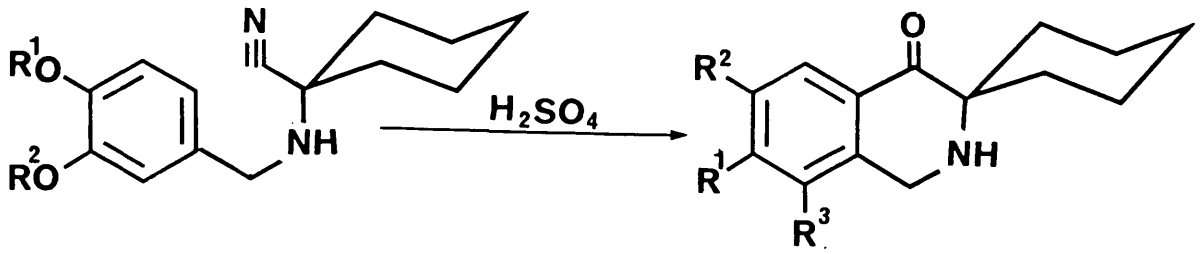
2,3-dihydro-6,7-dihydroxy-isoquinolin-4(1H)-one-3-spirocyclohexane



Scheme 55

The alkoxyhydroxyisoquinolinones isolated from these cyclisations have the orientation of C6 and C7 substituents consistent with the spirocyclic-intermediate.

The results obtained from the cyclisation of amino-nitriles (58-66) with a spirocyclohexyl substituent at C3 are summarised in scheme 56.



Nitrile	R^1	R^2	Compd.	R^1	R^2	R^3	Yield (%) at -10^o	R.T.	50^o
(58)	Me	Me	(79)	OMe	OMe	H	75	60	15
			(80)	OH	OMe	H	10	21	65
(59)	Et	Me	(81)	OEt	OMe	H	72	52	2.6
			(80)	OH	OMe	H	15	22	65
			(82)	OH	H	OMe	3	3.9	2.2
(60)	Me	Et	(83)	OMe	OEt	H	58	26	8
			(84)	Me	OH	H	0	25	48
			(85)	OH	OEt	H	32	35	0
(61)	H	Me	(80)	OH	OMe	H	86	80	70
			(82)	OH	H	OMe	4	3.9	3
			(86)	OH	OH	H	3	4	7
(62)	Me	H	(84)	OMe	OH	H	82	75	68
			(87)	OMe	H	OH	2.8	2.2	2.o
			(86)	OH	H	H	4	7	12
(63)	H	Et	(85)	OH	OEt	H	70	55	5
			(86)	OH	OH	H	5	10	18
(64)	Et	H	(88)	OEt	OH	H	60	34	3.2
			(86)	OH	OH	H	8	14	29
(65)	CD_3	Me	(89)	OCD_3	OMe	H	70	60	18
			(80)	OH	OMe	H	7	25	72
(66)	Me	CD_3	(90)	OMe	OCD_3	H	69	62	10
			(91)	OH	OMe	H	6	29	71

Scheme 56

2.5.0 Preparation and cyclisation of 2-(3,4-dialkoxybenzylamino)-2-benzylpropionitrile

As discussed in the introductory section, Harcourt, Taylor and Waigh have reported that cyclisation of 2-(3,4-dimethoxybenzylamino)-2-benzylpropionitrile (67) at 50° in concentrated sulphuric acid gave the 3-benzoyltetrahydroisoquinoline (92) as a sole product rather than the 3-benzylisoquinolinone.

However, although in the later communication these authors confirm this, but they also claimed that in the homologous nitrile (17, see page 31) an equimolecular mixture of 3-benzylisoquinolinone (19) and the dimethoxybenzcylisoquinolinone (20) were isolated.

In view of these results the present work was undertaken to evaluate the exact composition of the crude dialkoxy and phenolic products, obtained from cyclisation of aminonitrile (67).

To obtain evidence on the pathway(s) by which cyclisation proceeds, the cyclisation of the isomeric ethoxymethoxy analogues (68 and 69) was also performed.

2.5.1 Preparation of 2-(3,4-dimethoxybenzylamino)-2-benzylpropionitrile (67), 2-(4-ethoxy-3-methoxybenzylamino)-2-benzylpropionitrile (68) and 2-(3-ethoxy-4-methoxybenzylamino)-2-benzylpropionitrile (69)

The general procedure for the preparation of aminonitriles described above was again employed.

The spectroscopic data (tables, 7 and 8, pages 167 and 170) and the melting point of the 2-(3,4-dimethoxybenzylamino)-2-benzylpropionitrile (67) were consistent with that reported in the literature[64,65]. However, the spectroscopic data (tables 7 and 8 pages, 167 and 170) of the isomeric ethoxymethoxybenzylaminonitriles (68 and 69) were virtually identical and apart from the ethoxyl signal, the spectra were similar to the dimethoxybenzylaminonitrile (67).

2.5.2 Cyclisation of 2-(3,4-dimethoxybenzylamino)-2-benzylpropionitrile (67)

After treatment of the aminonitrile (67) with concentrated sulphuric acid, the reaction mixture was worked up for crude dialkoxy and phenolic products as described in the general procedure.

Dialkoxy Products

Thin layer chromatography and ^{1}H n.m.r. analysis revealed the presence of two dialkoxy products, which were separated by elution from a chromatographic column of silica gel. The major component under all temperatures of

cyclisation was clearly the 6,7-dimethoxyisoquinolinone (92).

The ^{1}H.n.m.r. spectrum (table 11, page 185) exhibited the characteristic low field singlets at δ 7.65 and 6.62 ppm for the C5 and C8 aromatic protons respectively.

The 3-benzyl substituent gave rise to a multiplet (5H) between δ 7.41-7.2 ppm and an AB quartet (24) between δ 3.52-2.73 ppm were assigned to the C1-methylene protons, the two methoxyl groups and the C3-methyl substituent respectively. The NH proton gave a singlet at δ 2.4 ppm which disappeared[a] after deuteration.

The infra-red spectrum of this product showed a strong absorption band at 1760cm^{-1} (carbonyl stretching) and a band of medium intensity at 3280cm^{-1} (NH stretching).

The mass spectrum (table 12, page 190) had M^{+} at m/z 311, the base peak at m/z 220 resulting from the loss of a benzyl radical and an ion at m/z 178 due to a retro Diels-Alder reaction of the molecular ion.

The minor dialkoxy product had melting point and the spectroscopic data (tables 15 and 16, pages 195 and 198) which were consistent with those reported by Harcourt, Taylor and Waigh[64,65] for the 3-(3,4-dimethoxybenzoyl)-3-methyl--1,2,3,4-tetrahydroisoquinoline (106).

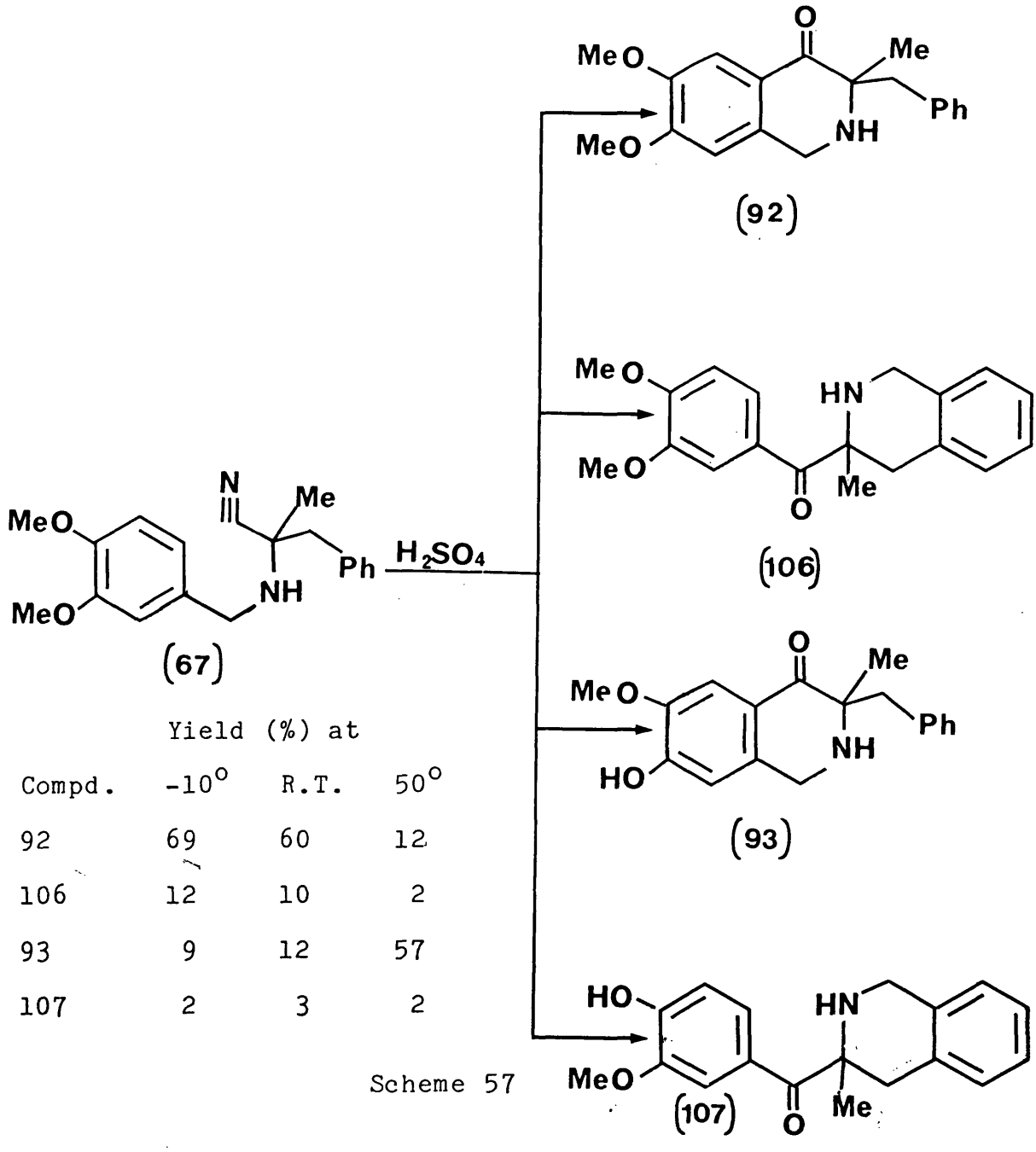
Phenolic Products

In a similar manner, chromatographic separation of the crude product gave the major component, the 7-hydroxy-6--methoxyisoquinolinone (93) and in a maximum yield of 3%, the 3-(4-hydroxy-3-methoxybenzoyl)-3-methyl-1,2,3,4-tetrahydroisoquinoline (107).

Apart from the presence of a singlet at 3.8 ppm for only one methoxy group, the ^{1}H n.m.r. spectra (tables 11 and 15, pages 185 and 195) of these two products closely corresponded to the dialkoxy counterparts.

Orientation of the phenolic hydroxyl group was established by ultra-violet spectroscopy and by the NaOD shift techniques (tables 11, 15 and 17, pages 195 and 199). Infra-red and mass spectra were unambiguous.

The results of this cyclisation are summarised in scheme 57.

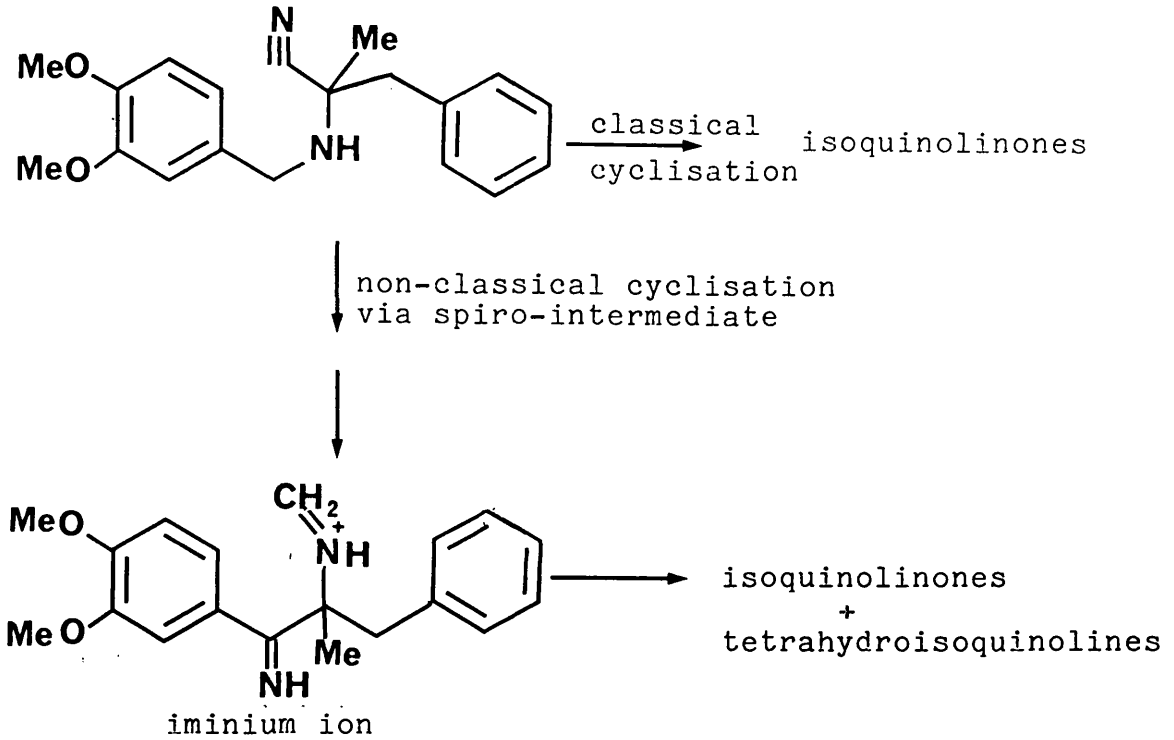


Compd.	Yield (%) at -10°	R.T.	50°
92	69	60	12
106	12	10	2
93	9	12	57
107	2	3	2

Scheme 57

Clearly, then cyclisation of the nitrile (67) is more complex than originally reported by Harcourt, Taylor and Waigh[64,65], who obtained as the sole product, the dimethoxybenzoyltetrahydroisoquinoline (106) in yields of 20-33%. It must be noted that these workers report no attempt to isolate phenolic products which in this reappraisal are produced even at -10°, and when cyclisation is carried out at 50°, the 7-hydroxy-6-methoxyisoquinolinone (93) forms the major product in 57% yield.

Furthermore the ratio of the isoquinolinone to tetrahydroisoquinoline is approximately 5:1, indicating that either classical cyclisation is making a significant contribution or that the iminium ion produced from the spiro-intermediate has a greater affinity for the dimethoxyphenyl group than the unactivated phenyl group, which is the alternative nucleophilic site (scheme 58).



Scheme 58

To assess the contribution that classical cyclisation is making, the corresponding ethoxymethoxybenzylaminonitriles were prepared and cyclised under the same conditions as above.

2.5.3 Cyclisation of 2-(4-ethoxy-3-methoxybenzylamino)--2-benzylpropionitrile (68)

Cyclisation and isolation of crude dialkoxy and crude phenolic products was carried out as before.

Dialkoxy Products

Separation by column chromatography (silica gel) gave two dialkoxy products. Cyclisation carried out at -10^{o} and room temperature yielded the 7-ethoxy-6-methoxy-isoquinolinone (94) as the major product. This differed in its ^{1}H n.m.r. spectrum (table 11, page 185) from the dimethoxy analogue (92) by the presence of only one methoxy signal (δ4.2-4.0 ppm, J = 7 Hz) and triplet (δ1.5-1.4 ppm, J = 7 Hz) characteristic of the ethoxy group.

The orientation of the C6 and C7 substituents was established by conversion of the isoquinolinones to the 4--benzyl-4-hydroxytetrahydroisoquinoline (122), which resulted in asignificant shift to higher field of the signal due to the C5-proton and that of the methoxyl group (table 19, page 206).

The minor product had a ^{1}H n.m.r. spectrum (table 15, page 185) characteristic for a 3-(ethoxymethoxybenzoyl)--3-methyl-1,2,3,4-tetrahydroisoquinoline. Here, the

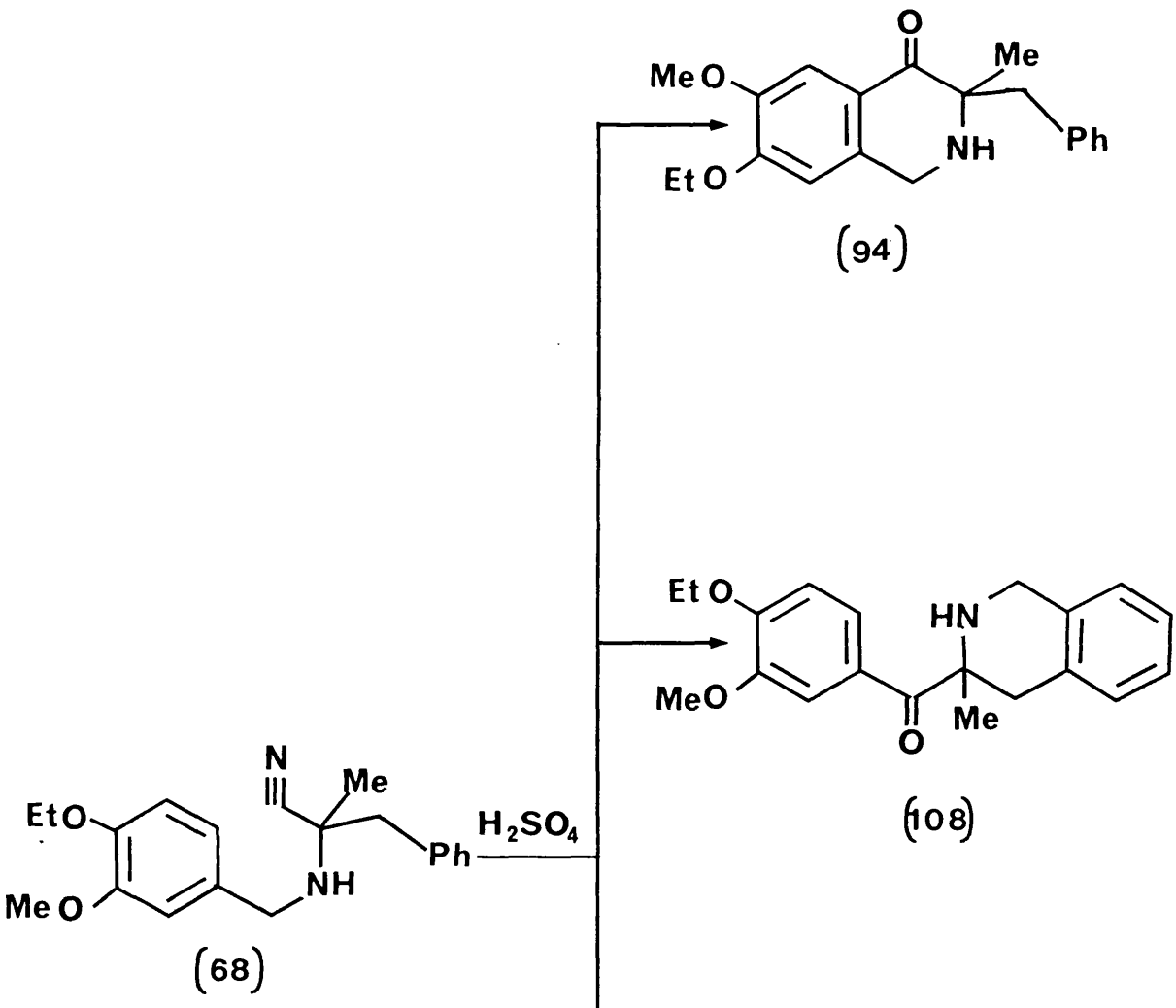
establishment of the orientation of the alkoxy substituents is not achieved as readily as in the case of the isoquinolinone. However, since it originates from the nitrile via the spiro-intermediate and iminium ion, the ethoxy substituent is presumably para to the carbonyl group.

Phenolic Products

Chromatographic separation of the crude product gave the 7-hydroxy-6-methoxyisoquinolinone (93) as the major product and a minor component the 3-(4-hydroxy-3-methoxybenzoyl) tetrahydroisoquinoline (107) in the ratio of five to one.

The spectroscopic data (tables 11 and 15, pages 185 and 195) and melting points of these products were identical with those phenolic products obtained from cyclisation of the dimethoxybenzylaminonitrile (67, page 103).

The yields of the phenolic and dialkoxy products depended upon the temperature of the cyclisation and are summarised in scheme 59.



Compd.	Yield (%) at -10°	R.T.	50°
94	60	50	2
108	14	10	0.4
93	9	20	62
107	2	4	16

Scheme 59

2.5.4 Cyclisation of 2-(3-ethoxy-4-methoxybenzylamino)--2-benzylpropionitrile (69)

Cyclisation of aminonitrile (69) was performed under identical conditions to those used for the isomeric aminonitrile (68). Isolation and separation of the crude dialkoxy and phenolic product was carried out as described above.

Dialkoxy Products

Separation (by column chromatography) of the crude dialkoxy product obtained from cyclisation performed at -10^{o} gave the 6-ethoxy-7-methoxyisoquinolinone (95) and the 3-(3-ethoxy-4-methoxybenzoyl) tetrahydroisoquinoline (111) in approximately 5:1 ratio (tables 9 and 13, pages 178 and 193). The same pattern of product ratio was obtained in repeated cyclisations with varied temperatures (i.e. room temperature and 50^{o}) and the results obtained are summarised in scheme 60.

There was insignificant difference between the spectroscopic data of these dialkoxyisoquinolinones and those of the isoquinolinones obtained by cyclisation of the isomeric dialkoxybenzylaminonitrile (68).

Phenolic Products

Separation of the crude product (by column chromatography) isolated from cyclisation carried out at -10^{o} gave the 6-ethoxy-7-hydroxyisoquinolinone (97) in 20% yield accompanied by a minor component, the 3-(3-ethoxy-

-4-hydroxybenzoyl) tetrahydroisoquinoline (111) in 4% yield.

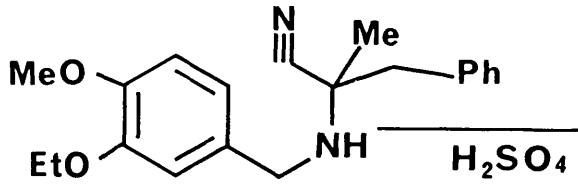
The ^{1}H n.m.r. spectra (tables 11 and 15, pages 186 and 196) of these phenolic products were similar to their hydroxymethoxy analogues (except for the orientation of the hydroxyl group) (93 and 107) respectively, except for the presence of a quartet and triplet, characteristic for the ethoxy substituent.

By comparison the crude phenolic product isolated from cyclisation performed at 50° gave, upon separation (as described above) a major product, namely the 6-hydroxy--7-methoxyisoquinolinone (96) and a minor product the 3-(3-hydroxy-4-methoxybenzoyl) tetrahydroisoquinoline (110), again in the ratio of five to one.

Infra-red, ^{1}H n.m.r. and mass spectra of these products were similar to their isomeric products (93 and 107) respectively, except for the orientation of the hydroxyl substituent.

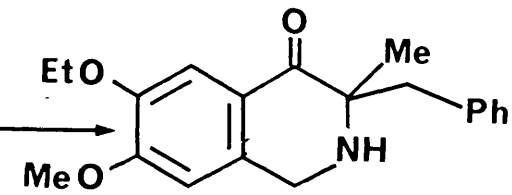
In contrast to cyclisation performed at the above temperatures, the cyclisation carried out at room temperature produced all four phenolic products. Again the ratio of isoquinolinones to tetrahydrosioquinolines being five to one. These results are shown in scheme 60.

Orientation of the hydroxyl substituent in these phenolic products (96,97, 110 and 111) was established by ultra-violet spectroscopy and NaOD shifts (tables 11,15 and 17 pages 186,196 and 199). Further confirmation of the structures (96 and 97) was obtained by converting the isoquinolinones to their 4-benzyl-4-hydroxytetrahydroisoquinolines (table 18, page 202).

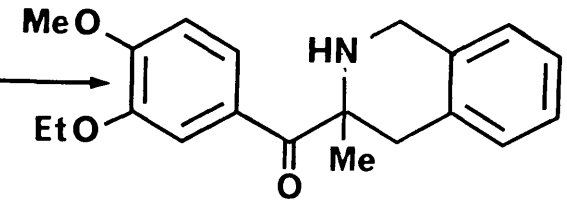


(69)

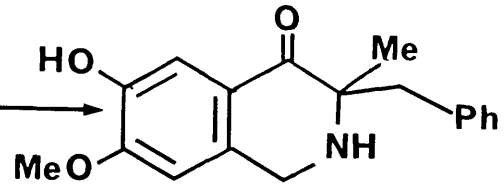
H_2SO_4



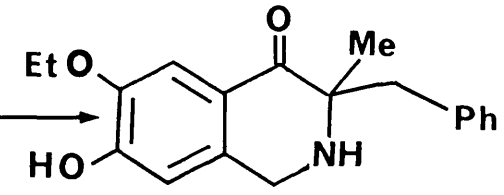
(95)



(109)

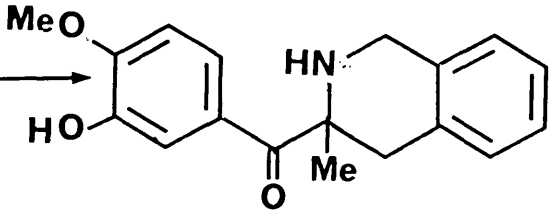


(96)

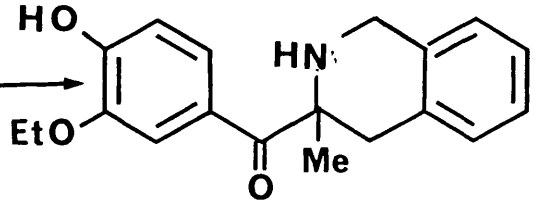


(97)

Compd.	Yield (%) at -10°	R.T.	50°
95	55	41	3
109	12	8	0.5
96	0	17	60
97	20	12	0
110	0	3.5	12
111	4	3	0



(110)



(111)

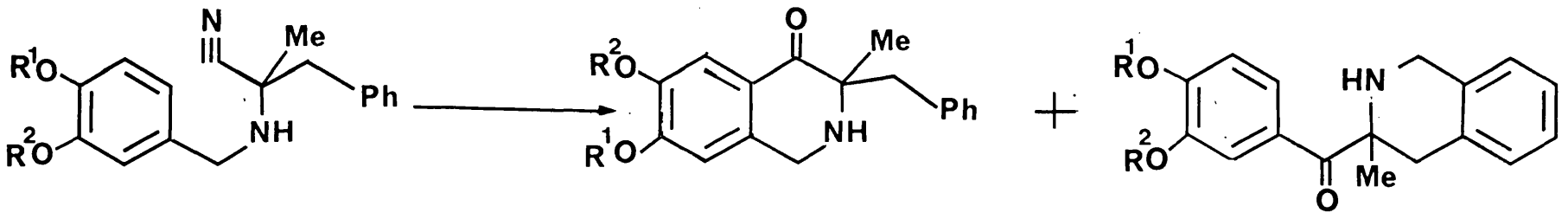
Scheme 60

The results obtained from the cyclisation of benzyl substituted aminonitriles (67, 68 and 69) at various temperatures (-10^{o}, R.T. and 50^{o}) are fully summarised in scheme 61. Together these results indicate that cyclisation of aminonitriles (67,68 and 69) proceeded exclusively via a spiro-intermediate. This then would ring open to yield the iminium ion (52) which could be attacked by either of the isomeric rings as competing nucleophiles resulting in isoquinolinones and tetrahydroisoquinolines.

However, since the ratio of isoquinolinones to tetrahydroisoquinolines are found to be five to one, it is therefore, clear that the iminium ion produced have greater preference for the more highly activated dialkoxyphenyl group as compared to the unactivated phenyl group (scheme 62).

The results, which show a consistent ratio of 5:1 in favour of the isoquinolinone over the tetrahydroisoquinoline, are in contrast to those reported by Harcourt and co-workers[64,65], whose work was discussed earlier (page 30).

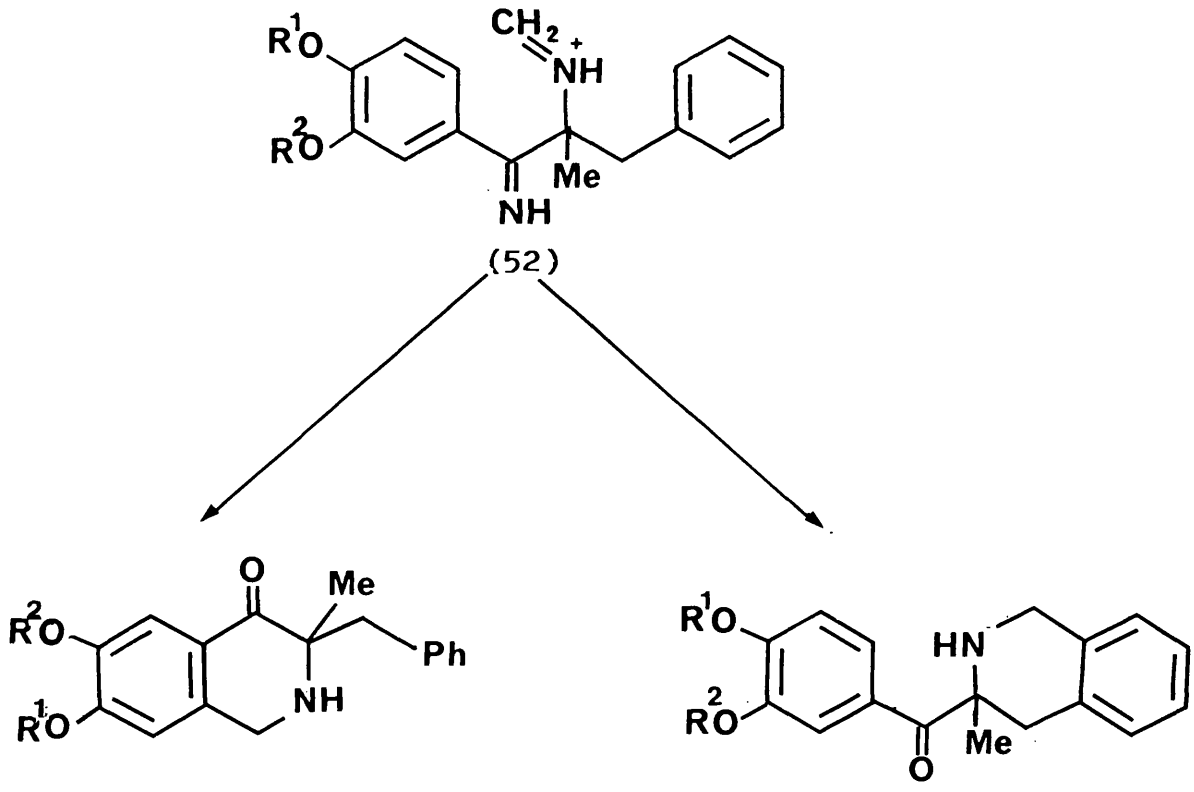
The pattern of O-dealkylation is closely similar to that observed for ethoxymethoxybenzylaminocyclohexane carbonitriles (59 and 60), with the formation of ethoxy-hydroxy phenolic products at the lower temperatures in the case where the ethoxy group is not participating in formation of the spiro-intermediate.



92–97 106 – 111

Nitrile	R^1	R^2	Compd.	R^1	R^2	Yield (%) at -10°	R.T.	50°	Compd.	R^1	R^2	Yield (%) at -10°	R.T.	50°
67	Me	Me	92	Me	Me	69	60	12	106	Me	Me	12	10	2
	Veratraldehyde Series		93	H	Me	9	12	57	107	H	Me	2	3	2
68	Et	Me	93	H	Me	9	20	62	107	H	Me	2	4	16
	Vanillin Series		94	Et	Me	60	50	2	108	Et	Me	14	10	0.4
69	Me	Et	95	Me	Et	55	41	3	109	Me	Et	12	8	0.5
	Isovanillin Series		96	Me	H	0	17	60	110	Me	H	0	3.5	12
			97	H	Et	20	12	0	111	H	Et	4	3	0

Scheme 61



Compound	R^1	R^2		Compound	R^1	R^2
92	Me	Me	Veratraldehyde	106	Me	Me
93	H	Me	Series	107	H	Me
93	H	Me	Vanillin	107	H	Me
94	Et	Me	Series	108	Et	Me
95	Me	Et	Isovanillin	109	Me	Et
96	Me	H	Series	110	Me	H
97	H	Et		111	H	Et

Scheme 62

2.6.0 Preparation and cyclisation of 2-(4-ethoxybenzylamino)-2-benzylpropionitrile

The formation of a spiro-intermediate in cyclisation of benzylaminonitriles, as discussed above, requires only the para-alkoxy substituent to produce the iminium ion via the spiro-intermediate. The iminium ion thus formed has been reported to undergo attack by the imino group to form imidazolines[66] (in the absence of an alternative nuclophile)

However, where alternative nucleophilic sites are present (such asabenzyl substituent), it appears that Pictet-Spengler cyclisation of this intermediate iminium ion to the benzyl substituent led to the formation of 3-benzoyltetrahydroisoquinolines[64,65] . For example, as discussed in the introductory section (page 32) the 2-(4-methoxybenzylamino)-2-benzylpropionitrile (19), upon treatment with sulphuric acid at 50° or room temperature gave exclusively the methoxybenzoyltetrahydroisoquinoline (21) in 73% yield.

Since there was no report on the isolation of imidazoline from this reaction , it led the present worker to investigate the cyclisation of this type of aminonitrile, in order to more fully assess the competition between formation of a tetrahydroisoquinoline and a 3-imidazoline.

2.6.1 Preparation of 2-(4-ethoxybenzylamino)-2-benzyl-propionitrile (73)

The 4-ethoxybenzylaminonitrile (73) was prepared in excellent yield by the general method (as previously discussed) from 4-ethoxybenzyaldehyde.

The Infra-red spectrum showed characteristic nitrile stretching at 2250cm^{-1} and -NH stretching at 3360cm^{-1}. The ^{1}H n.m.r. spectrum exhibited the $AA^{1}xx^{1}$ spin pattern of the para disubstituted benzene ring as two doublets at δ 7.24-7.12 and δ 6.83-6.40 ppm. The protons of the phenyl group resonated as a complex multiplet at low field δ 7.32-7.25 ppm, while the ethoxy group gave rise to a characteristic quartet and triplet at δ 4.10-3.82 and δ 1.40-1.24 ppm respectively.

The benzylamino methylene protons gave rise to a singlet at δ 3.76 ppm; singlets also being observed for the other benzylic protons (δ 2.9 ppm), the methyl group (1.36 ppm) and the exchangable proton of the amino group (1.52 ppm).

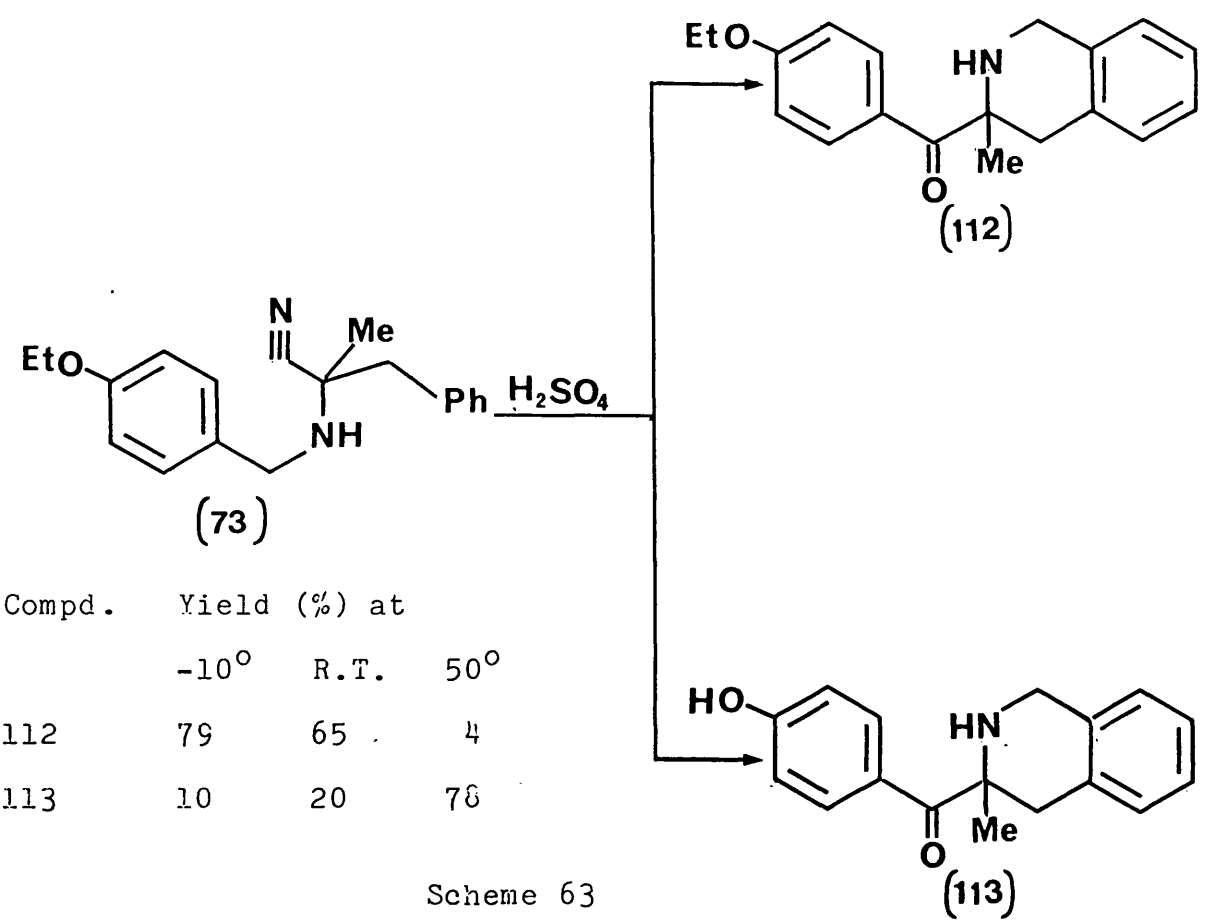
The Mass spectrum showed the molecular ion (M^{+}) at m/z 294 (low eV), a peak at m/z 267 due to loss of HCN from molecular ion and a base peak at m/z 135 (70 eV) due to the 4-ethoxybenzyl cation (which presumably would have rearranged to the ethoxytropylium ion).

2.6.2 Cyclisation of 2-(4-ethoxybenzylamino)-2-benzyl-propionitrile (73)

Cyclisation of 4-ethoxybenzylaminonitrile (73) was carried out at -10°, room temperature and 50° in concentrated sulphuric acid.

Analysis of the resulting crude alkoxy and phenolic product (from each cyclisation) by thin layer chromatography revealed only one spot.

Thus cyclisation of aminonitrile (73) at the above temperature gave the 3-(4-ethoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline (112) and 3-)4-hydroxybenzoyl)-1,2,3,4-tetrahydroisoquinoline (113), the phenolic product being formed almost exclusively at 50° (table 13, page 193, and scheme 63).



(73) (112) (113)

Compd.	Yield (%) at		
	-10°	R.T.	50°
112	79	65	4
113	10	20	78

Scheme 63

The preferance for the formation of the tetrahydro-isoquinolines over the 3-imidazolines from this type of aminonitrile is probably because the formation of a five membered ring is energetically less favourable than formation of a six membered ring.

The products (112 and 113) were identified from their ^1H n.m.r. spectrum, infra-red spectrum and mass spectrum. The mass spectrum of (112) exhibited a fairly weak molecular ion at m/z 295 (low eV) and base peak at m/z 146 (70 eV). The ^1H n.m.r. spectrum exhibited a AA^1xx^1 spin pattern of the para disubstituted benzene ring as two doublets at δ 8.4-8.26 and δ6.82-6.72 ppm.

The four aromatic protons of an isoquinoline ring resonated between δ 7.12 and 6.90 ppm, whereas an ethoxyl group gave rise to a low field quartet (δ4.0-3.84) and a high field triplet (δ1.38-1.24 ppm) with a coupling constant of 8 Hz.

An AB quartet for the C4 protons was observed between δ3.52-2.45 ppm. The three singlets due to the C1-protons, a deuterable proton of the secondary amine and the methyl group appeared at δ3.82 and 1.48 ppm respectively.

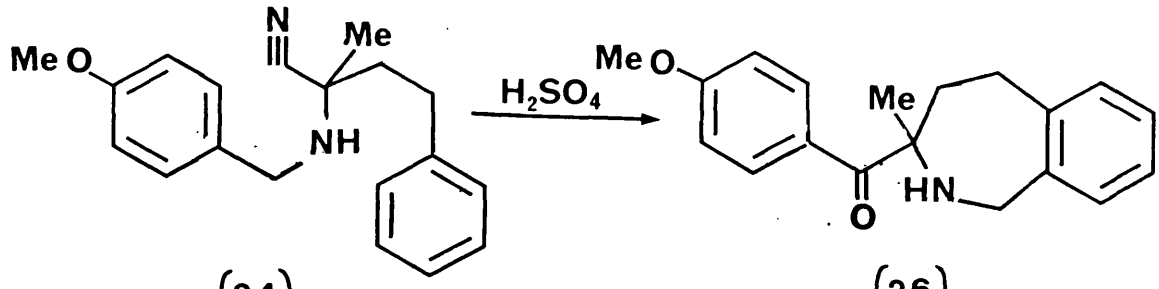
The Infra-red spectrum displayed a strong carbonyl absorption at 1680cm^{-1}.

The ^1H n.m.r. of the phenolic product (113) was similar to its alkoxy analogue except for the absence of signals due to the ethoxy group.

The Infra-red and mass spectra (tables 15 and 16, pages 197 and 198) were unambigious.

2.7.0 Preparation and cyclisation of 2-(3,4-dialkoxybenzylamino)-2-methyl-4-phenylbutyronitriles

Previous work[65] has shown that the aminonitrile (24) cyclises in concentrated sulphuric acid to give benzazepine (26) via the spiro-intermediate (see page 34).



(24) (26)

In view of this finding, the cyclisation of aminonitrile derived from veratraldehyde and the isomeric ethoxymethoxybenzaldehydes were investigated.

2.7.1 Preparation of 2-(3,4-dialkoxybenzylamino)-2-methyl-4-phenylbutyronntriles (70,71 and 72)

The general procedure for the preparation of aminonitriles discussed above (section 2.0.1, page 49) was again employed.

The ^{1}H n.m.r. spectrum (table 7, page 167) of the 2-(3,4-dimethoxybenzylamino)-2-methyl-4-phenylbutyronitrile (70) exhibited a complex multiplet (integrating to five

protons) at low field (δ7.25-7.04 ppm) due to the aromatic protons of the phenethyl moiety. The three protons of the 1,3,4-trisubstituted benzene ring resonated between δ6.90 and 6.70 ppm, while the two methoxyl groups and methylene protons adjacent to the nitrogen appeared as a strong singlet at δ3.80 ppm. The two methylene groups of the phenethyl moiety appeared as two groups of multiplets (arising from chirality at C3) at δ2.90-2.64 ppm ($-CH_2-\underline{CH_2}-Ar$), and between δ2.06-1.84 ppm ($-\underline{CH_2}-CH_2Ar$). A deuterable proton of the secendary amine and methyl group gave singlets at δ1.6 and 1.48 ppm respectively.

An electron impact mass spectrum exhibited the molecular ion (M^+) at m/z 324 (low eV) and the base peak at m/z 151 (70 eV).

The ^{1}H n.m.r. spectra (table 7, page 168) of the two isomeric aminonitriles, namely the 2-(4-ethoxy-3-methoxybenzylamino)-2-methyl-4-phenylbutyronitrile (71) and 2-(3-ethoxy-4-methoxybenzylamino)-2-methyl-4-phenylbutyronitrile (72) were virtually identical. Furthermore, these aminonitriles (71 and 72) differed in their ^{1}H n.m.r. spectra from the dimethoxy analogue (70) by the presence of only one methoxy signal (δ3.80 ppm) and the appearance of a quartet (δ4.10-3.90 ppm) and triplet (δ1.49-1.15 ppm) with coupling constant of 8 Hz, characteristic for the ethoxyl group. The Infra-red and mass spectra were unambiguous.

2.7.2 Cyclisation of 2-(3,4-dimethoxybenzylamino) -2-methyl-4-phenylbutyronitrile(70)

The aminonitrile (70) was treated with concentrated sulphuric acid and the reaction mixture was worked up for crude dialkoxy and phenolic product, as described previously (section 2.0.2, page 49).

Dialkoxyisoquinolinones

Thin layer chromatographic analysis of the crude dialkoxy product revealed two components, which were separated by fractional recrystallisation using a mixture of petroleum-ether (60-80°) and ethylacetate (1:1).

The major product had ^{1}H n.m.r. spectrum (table 11, page 186) which exhibited the normal singlet for the C5 and C8 protons at δ 7.52 and 6.50 ppm respectively, whereas the five aromatic protons of the phenethyl group appeared as a complex multiplet between δ 7.24 and 7.18 ppm. The singlets due to the C1 protons, the two methoxyl groups, the deuterable proton of the secondary amine and methyl group appeared at δ 4.07, 3.88, 2.34 and 1.37 ppm respectively.

However, the two methylene groups of the phenethyl moiety gave rise to triplet (δ2.80-2.62 ppm, $-CH_2$ $-\underline{CH_2}$-Ar) and a complex multiplet (δ2.20-1.80 ppm, $-\underline{CH_2}$ $-CH_2$-Ar).

By comparison the ^{1}H.n.m.r. spectrum (table 11, page 187), of the minor component showed two doublets (J = 8 Hz) at δ 7.88-7.78 and δ 6.68-6.58 ppm due to the C5-H and

C6-H respectively of the 7,8-disubstituted isoquinolinone (99). This is another example of an atypical Pictet-Spengler cyclisation of the iminium ion ortho to an alkoxy substituent. The rest of the spectrum was similar to the isomeric 6,7-dimethoxyisoquinolinone (98).

Infra-red and mass spectra (tables 11 and 12, pages, 186 187 and 191) of these dialkoxyisoquinolinones were unambiguous.

Phenolic Isoquinolinones

In a similar way, fractional recrystallisation of the crude phenolic product resulted in a major component, the 7-hydroxy-6-methoxyisoquinolinone (101) and a 7-hydroxy--8-methoxyisoquinolinone (100).

Apart from the presence of a singlet at δ 3.8 ppm, for only one methoxyl group, the ^{1}H n.m.r. spectra (table 11, page 187) of these phenolic isoquinolinones were similar to their dialkoxy analogues.

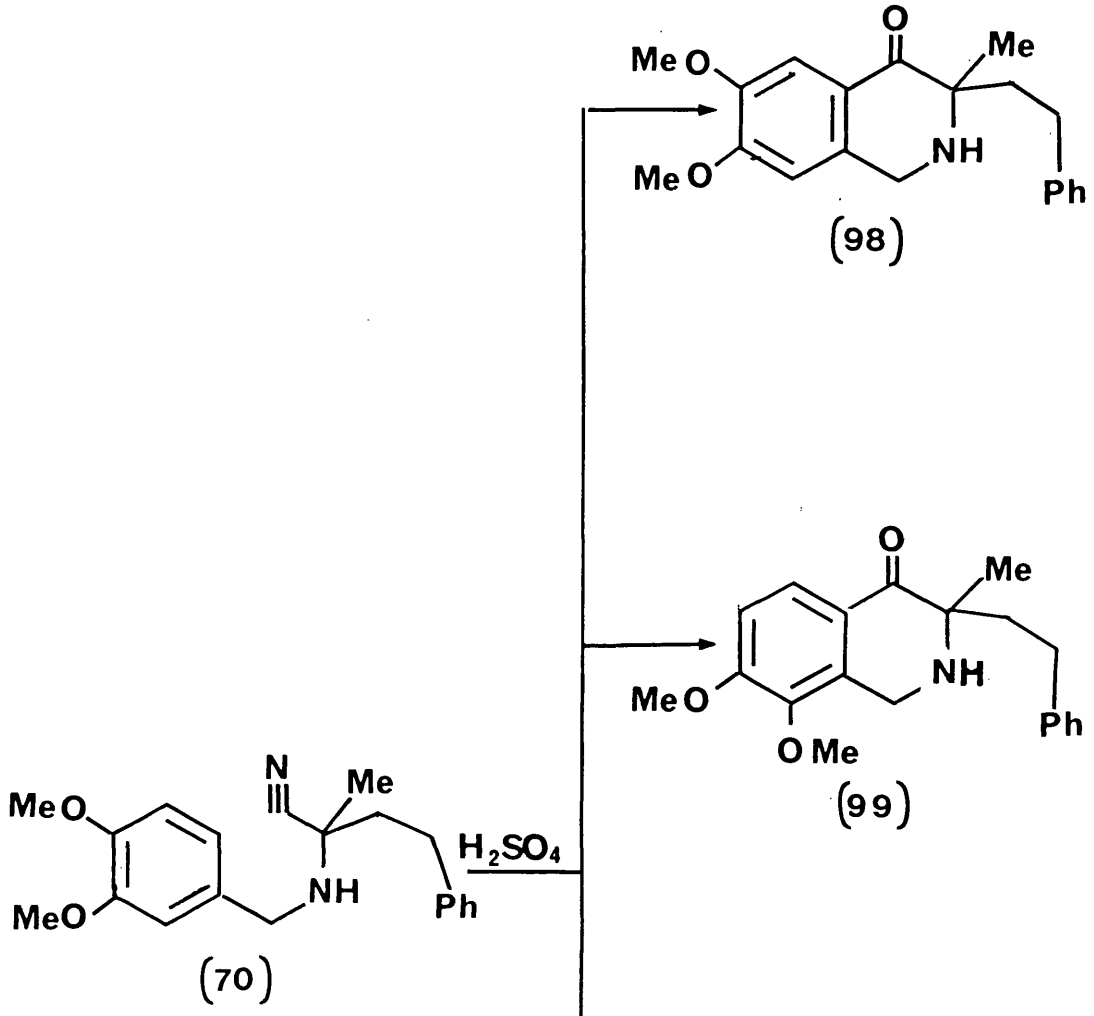
The orientation of the hydroxymethoxy substituents was established by ultra-violet spectroscopy and the NaOD shift technique and in addition, the structure of phenolic isoquinolinone (101) was confirmed by preparing the 4-benzyl-4-hydroxytetrahydroisoquinoline (129, tables 18-20, pages 203,208 and 212).

The ^{1}H n.m.r. spectrum (table 11, page 187) of the 7-hydroxy-6-methoxyisoquinolinone (101) exhibited the characteristic low field singlets at δ 7.42 and δ 6.69 ppm for the C5 and C8 aromatic protons respectively, which upon treatment with NaOD in D_2O underwent upfield shifts

to δ 7.26 and δ 6.00 ppm, representing an upfield shift of 16 Hz and 69 Hz respectively. The phenolic hydroxyl group is therefore located at C7.

The minor phenolic isoquinolinone (100) showed two doublets (J = 8 Hz) centred at δ 7.78 and δ 6.51 ppm for the C5 and C6 aromatic protons respectively. On addition of NaOD in D_2O the two doublets moved to higher field (δ7.53, C5-H and δ 5.91, C6-H) representing an upfield shift of 35 Hz and 60 Hz respectively, showing that the phenolic hydroxyl substituent is at C7.

The above results are summarised in scheme 64.



Compd.	Yield (%) at		
	-10°	R.T.	50°
98	54	49	8
99	3.9	2.5	1.2
101	7	14	40
100	1.3	2.1	3.2

Scheme 64

2.7.3 Cyclisation of 2-(4-ethoxy-3-methoxybenzylamino)--2-methyl-4-phenylbutyronitrile (71) and 2-(3--ethoxy-4-methoxybenzylamino)-2-methyl-4-phenylbutyronitrile (72)

Treatment of benzylaminonitrile (71) with concentrated sulphuric acid and isolation of crude dialkoxy and phenolic product(s) was performed as described above.

Fractional recrystallisation of the crude dialkoxy product gave a single dialkoxyisoquinolinone, which differed in its ^{1}H n.m.r. spectrum (table 11, page 187) from the dimethoxy analogue (98) by the presence of only one methoxyl signal (δ3.88 ppm) and the appearance of a quartet (δ4.2-4.0 ppm, J = 7 Hz), and triplet (δ1.5-1.4 ppm, J = 7 Hz) characteristic for the ethoxy substituent.

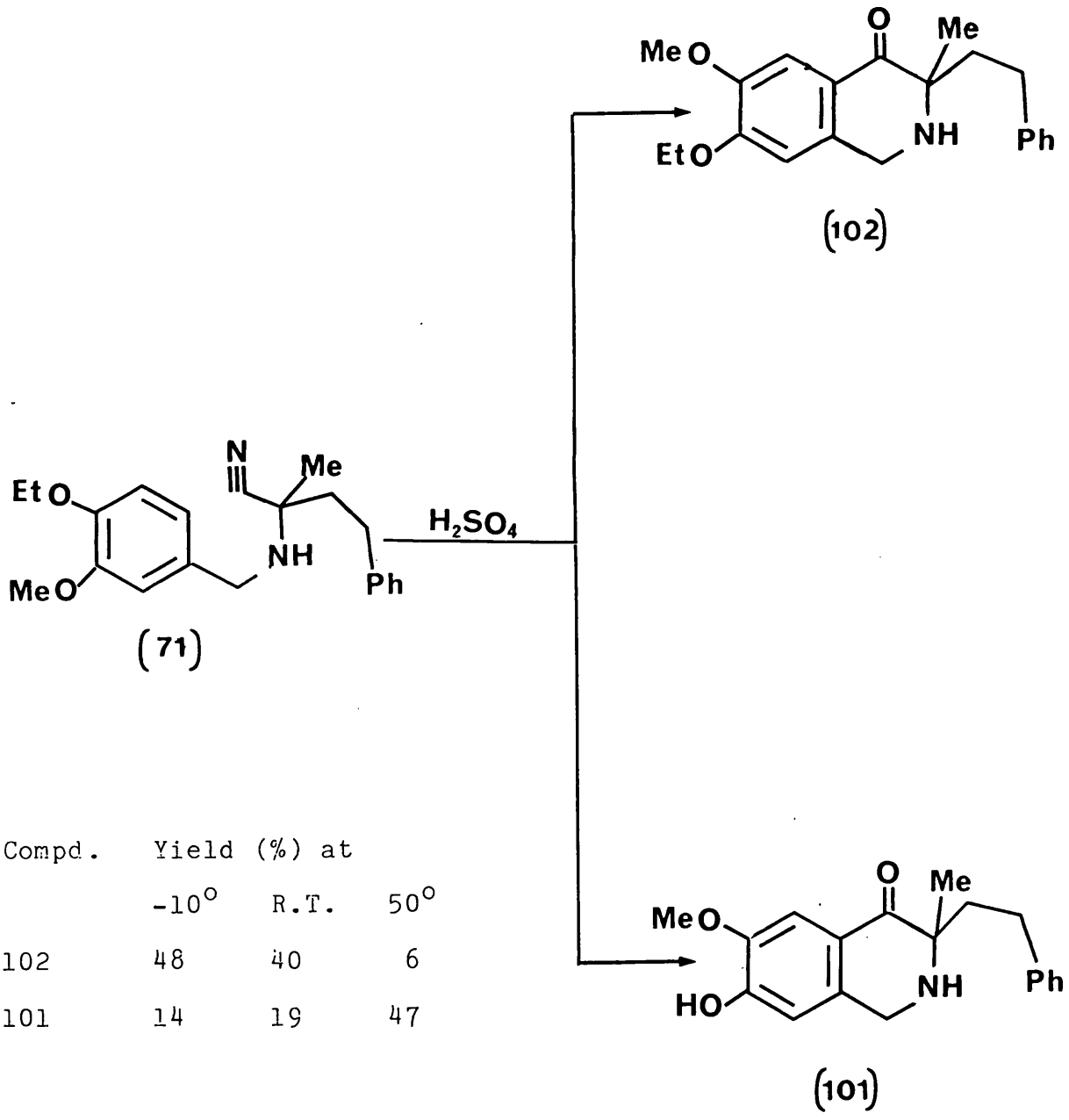
The orientation of the dialkoxy substituents was established by introducing the benzyl substituent at the C4 position, by means of the Grignard reaction.

The spectroscopic data (tables 19,20, pages 208 and 212) of this 4-benzyl-4-hydroxytetrahydroisoquinoline (128) clearly show significant shift to higher field of the signal due to the C5 proton and that of the methoxyl group which therefore must be located at C6.

Similarly a single phenolic product was obtained at all temperatures (scheme 65), which had melting point and spectroscopic data identical to those of 7-hydroxy-6--methoxyisoquinolinone (101).

The orientation of the hydroxy and methoxy substituents was established by means of ultra-violet spectroscopy and

the NaOD shift technique, which clearly shows the location of the hydroxyl group at C7.



Compd.	Yield (%) at		
	-10°	R.T.	50°
102	48	40	6
101	14	19	47

Scheme 65

By comparison cyclisation of the isomeric amino-nitrile (72) at room temperature gave a single dialkoxy-isoquinolinone, whose ^{1}H n.m.r. spectrum was identical to 7-ethoxy-6-methoxyisoquinolinone (102).

However, upon establishing the orientation of C6 and C7-substituents (by preparing the 4-benzyl-4-hydroxyisoquino-line, (tables 18-20, pages 203,209 and 212) the dialkoxyiso-quinolinone isolated from this reaction was shown to be 6-ethoxy-7-methoxyisoquinolinone (103).

The infra-red and mass spectra were unambiguous.

Thin layer chromatograpy of the crude phenolic product revealed to consist two components, which were separated by fractional recrystallisation using petroleum-ether (60-80°)/ethylacetate (3:1).

The ^{1}H n.m.r. spectrum (table 11, page 188) of the major component exhibited two singlets at δ 7.40 and δ 6.68 ppm for the C5 and C8 aromatic protons, which on addition of NaOD in D_2O underwent upfield shifts of 68 Hz and 23 Hz respectively. Thus confirming the location of the phenolic hydroxy substituent at C6. This was confirmed by ultra-violet spectroscopy which showed the phenolic group to be para to the C4 carbonyl function. Further confirmation towards the structure was obtained by preparing 4-benzyl--4-hydroxytetrahydroisoquinoline (131, tables 18-20, pages 204,209 and 213), which resulted inasignificant shift to higher field of the signal due to C5-H but not of the methoxyl group. The remaining part of the spectrum was identical to its isomeric phenolic isoquinolinone (101).

The minor component was the 6-ethoxy-7-hydroxy-

isoquinolinone (105) which differed in its ^{1}H n.m.r. spectrum (table 11, page 188) from the hydroxymethoxy and analogue (101) by the presence of a quartet (δ4.2-4.0 ppm, J = 7 Hz) and a triplet at (δ1.5-1.4 ppm, J = 7 Hz) characteristic of an ethoxy group.

The orientation of C6 and C7 substituents was established by ultra-violet spectroscopy (table 17, page 200) and the NaOD shift technique, which showed the hydroxyl group at C7.

However, cyclisation at -10° gave in addition to a single dialkoxyisoquinolinone, namely 6-ethoxy-7-methoxy-isoquinolinone (103), a single phenolic isoquinolinone, which had melting point and spectroscopic data consistent with the structure assigned to the 6-ethoxy-7-hydroxy-isoquinolinone (105). In contrast the cyclisation at 50° gave in addition to a low yield of the dialkoxyisoquinolinone (103), a single phenolic isoquinolinone, which was found to be the 6-hydroxy-7-methoxyisoquinolinone (104). This assignment was based upon ^{1}H n.m.r. NaOD shift measurements and ultra-violet spectroscopy (pages 188 and 200)

The yields obtained at three different temperatures are summarised in scheme 66 (page 129).

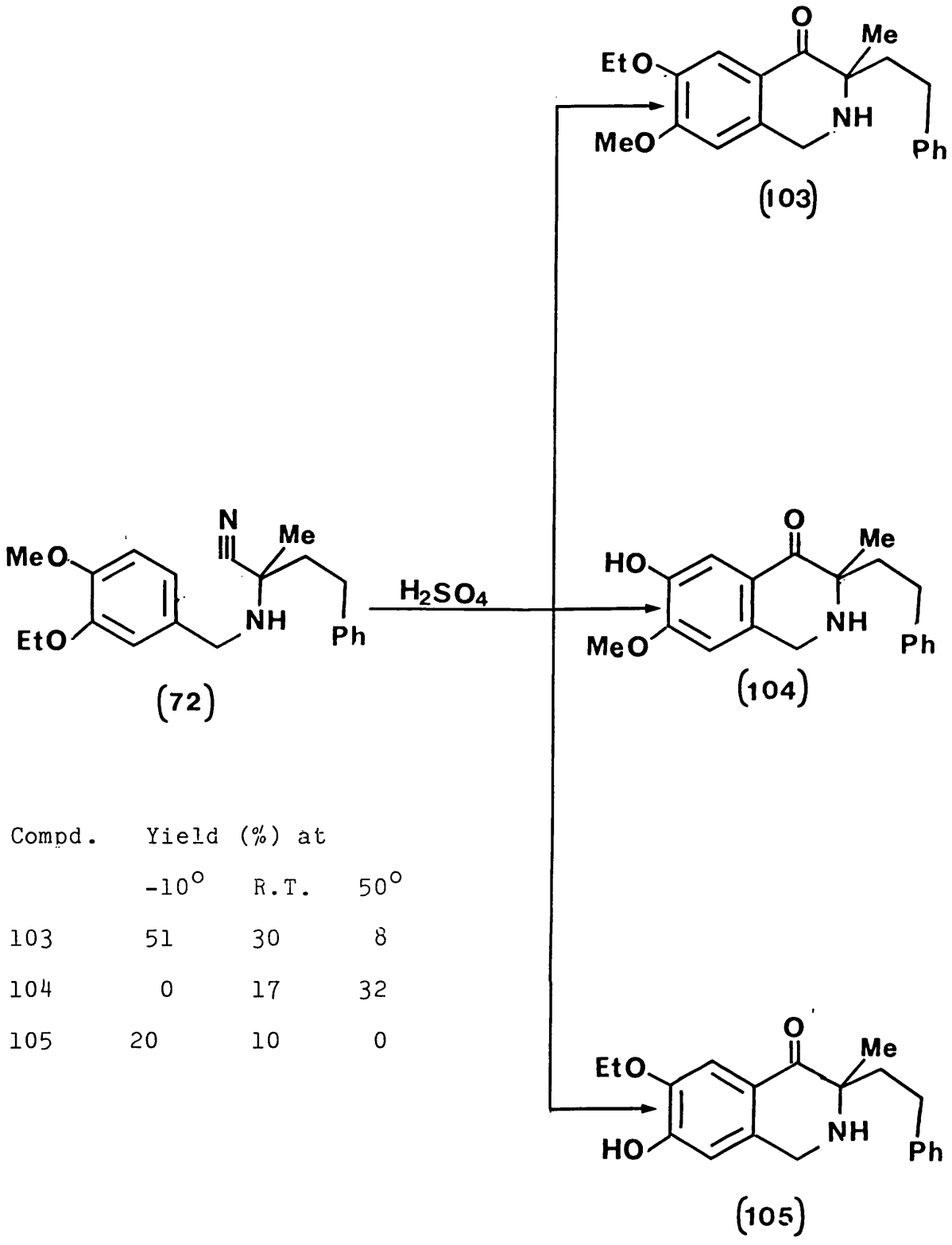
The above indicate that upon introducing a second alkoxy substituent in the aromatic ring (ortho to the first) a complete change in the course of the cyclisation results, yielding isoquinolinones rather than 2-benzazepines. This clearly demonstrates the ability of the C3-alkoxy substituent to participate in the Pictet-Spengler cyclisation of the iminium ion (by creating an increased

electron density at the point of ring closure).

This observation also suggests the greater difficulty of effecting the Pictet-Spengler cyclisation to produce a seven membered ring, especially when the phenethyl group lacks alkoxy substituents in the ring. It would be interesting to fully investigate the cyclisation of this type of nitrile where both alternative nucleophiles have suitably orientated activating substituents, since it has been reported that the yield of benzazepine may be increased from 5% to 50% by such a modification to the phenethyl aromatic ring[65].

Although the products obtained had orientation of the C6 and C7 substituents identical to those of the spiro-cyclohexyl analogues (pages 62 - 72), and are consistent with formation via the spirocyclic intermediates, the total recovery from the above cyclisations is lower.

The possible reason (as reported by Harcourt and co-workers) is that sulphonation of the phenethyl aromatic ring occurs. The aminosulphonic acid thus formed is likely to be difficult to isolate.



Compd.	Yield (%) at		
	-10°	R.T.	50°
103	51	30	8
104	0	17	32
105	20	10	0

Scheme 66

2.8.0 Preparation and cyclisation of 4-alkoxy-benzylaminoacetonitriles

Cyclisation of this type of aminonitrile was investigated to determine the effect of a C3-substituent on the cleavage of the C4-alkoxy group.

It was thought that increasing the steric crowding of the C4 alkoxy substituent might be a feature affecting the ease of de-alkylation. Thus preparation and cyclisation of 4-alkoxybenzylaminonitrile and 4-ethoxy-3-methyl analogue was carried out to compare the results obtained.

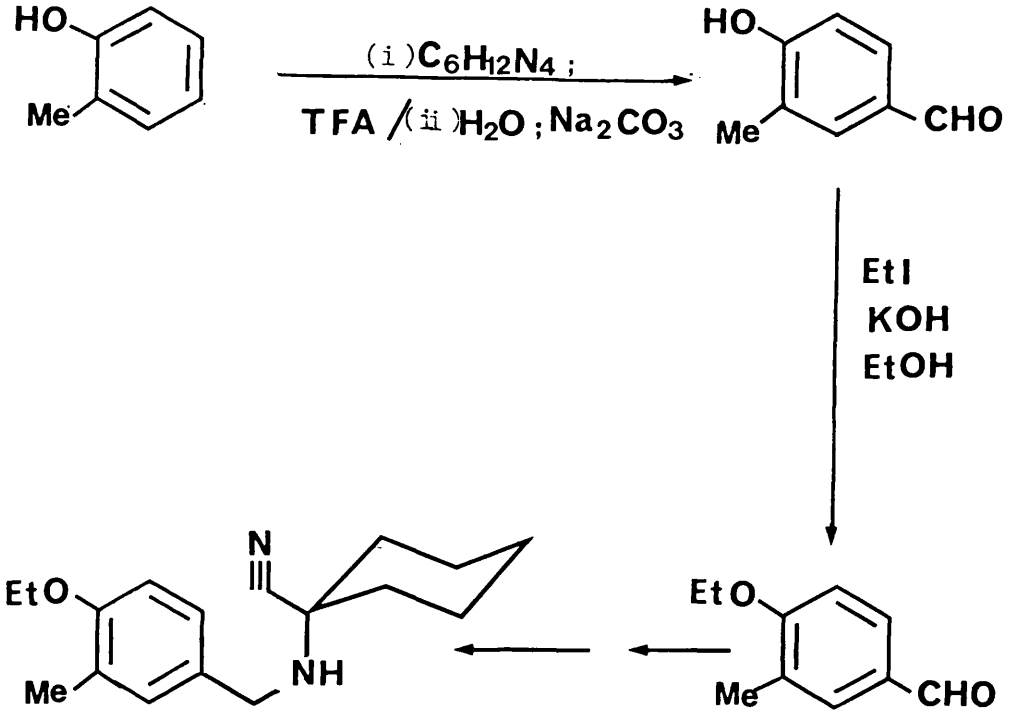
2.8.1 Preparation of 1-(4-methoxybenzylamino) cyclohexane carbonitrile (74) and 1-(4-ethoxybenzylamino) cyclohexane carbonitrile (75)

The benzylaminonitriles (74 and 75) were prepared from 4-methoxy and 4-ethoxybenzyldehyde respectively by the standard procedure discussed on page 86). The spectroscopic data (tables 7 and 8 , pages 168 and 171) and the melting point of aminonitrile (74) were consistent with published data[66].

The ^{1}H n.m.r. spectra of these nitriles differed only in the signals due to the alkoxy groups; a singlet (δ3.85 ppm) appearing for the methoxy group in (74) and the usual quartet (δ4.4-3.84 ppm) and triplet (δ1.40-1.22 ppm, J = 8 Hz) in the spectrum of the ethoxyaminonitrile (75).

2.8.2 Preparation of 1-(4-ethoxy-3-methylbenzyl-amino) cyclohexane carbonitrile (76)

The aminonitrile (76) was prepared in excellent yield from 4-hydroxy-3-methylbenzaldehyde[100] by the usual procedure (scheme 67).



Scheme 67

The ^1H n.m.r. spectrum of this aminonitrile (76) exhibited the low field multiplet (δ7.12-6.60 ppm) integrating to three aromatic protons.

The ethoxyl group gave rise to a quartet (δ4.40-3.85 ppm) and a triplet (δ1.40-1.28 ppm) with coupling constant of 8 Hz. The singlets due to methylene protons and methyl group appeared at δ 3.7 and 2.2 ppm respectively.

A broad singlet was observed between δ 2.0 and 1.4 ppm relating to cyclohexyl group and a deuterable proton of the secondary amine.

Infra-red and mass spectra were consistent with the structure assigned.

2.8.3 Preparation of 1-(3-methoxybenzylamino) cyclohexane carbonitrile (77) and 1-(2--ethoxybenzylamino) cyclohexane (78)

The aminonitriles (77 and 78) were prepared from 3-methoxybenzaldehyde and 2-ethoxybenzaldehyde respectively by a standard procedure (page 86).

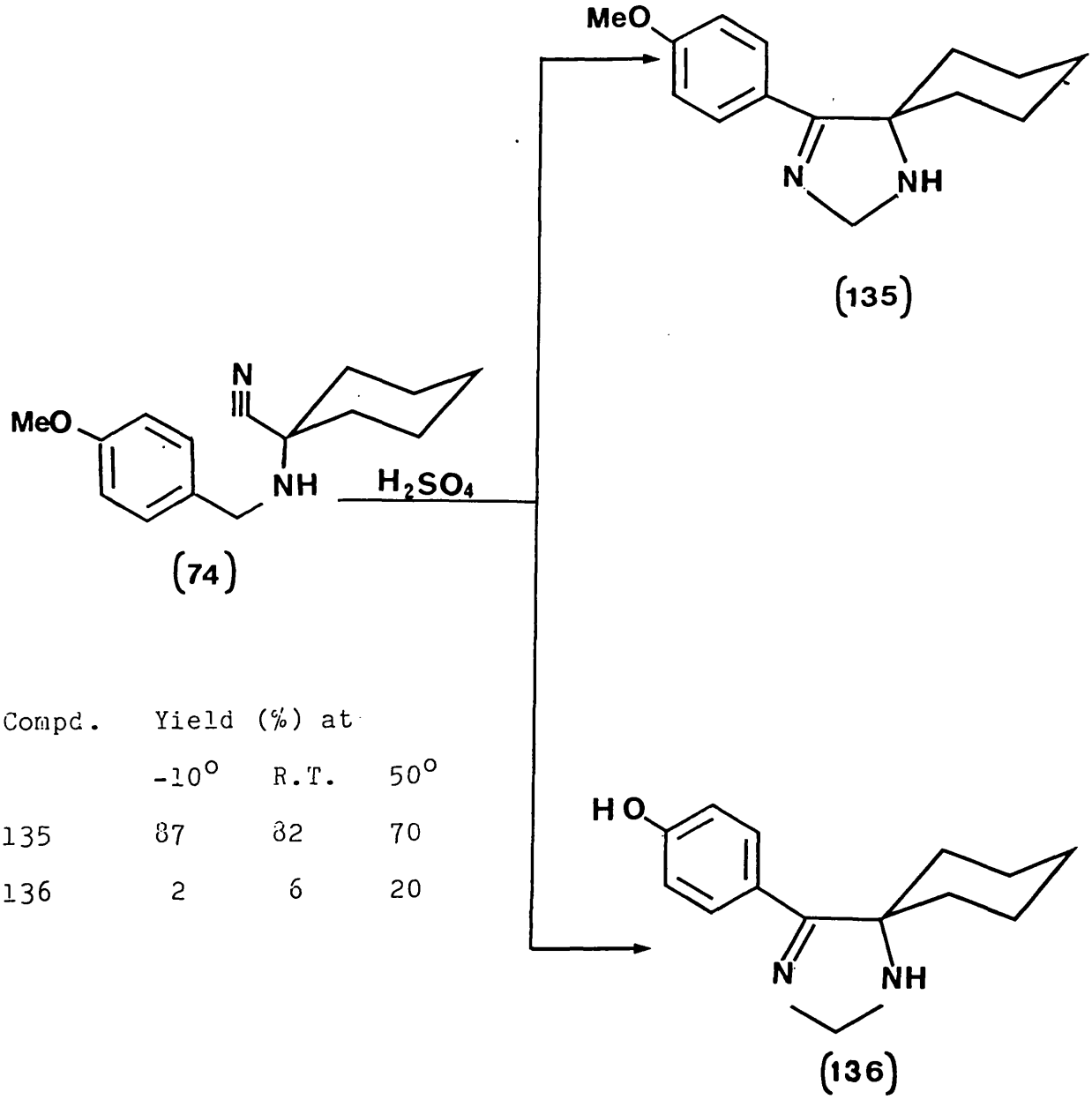
Spectroscopic data (tables 7 and 8, pages 169 and 171) for the aminonitrile (77) were consistent with previous reports[51]. The structure of aminonitrile (78) was confirmed by its spectroscopic and elemental analysis.

2.8.4 Cyclisation of 1-(4-methoxybenzylamino) cyclohexane carbonitrile (74) and 1-(4--ethoxybenzylamino cyclohexane carbonitrile (75)

Cyclisation of aminonitrile (74 and 75) was effected with concentrated (98%) sulphuric acid at -10°, room temperature and 50°.

Thus cyclisation of aminonitrile (74) gave, at all temperatures, a single alkoxy product, which had melting point and spectroscopic data (pages 217 and 218) consistent with those reported by Harcourt, Taylor and Waigh[66]

for the 3-imidazoline (135). However, in addition to this product, a single phenolic component was also isolated whose yield varied with the temperature of the cyclisation (scheme 68), Apart from the absence of signal due to an alkoxy group, the ^{1}H.n.m.r. spectrum (table 23, page 218) of the phenolic product was similar to its methoxy analogue (135). Infra-red and mass spectra (tables 23 and 24, pages 218 and 219) were unambiguous.



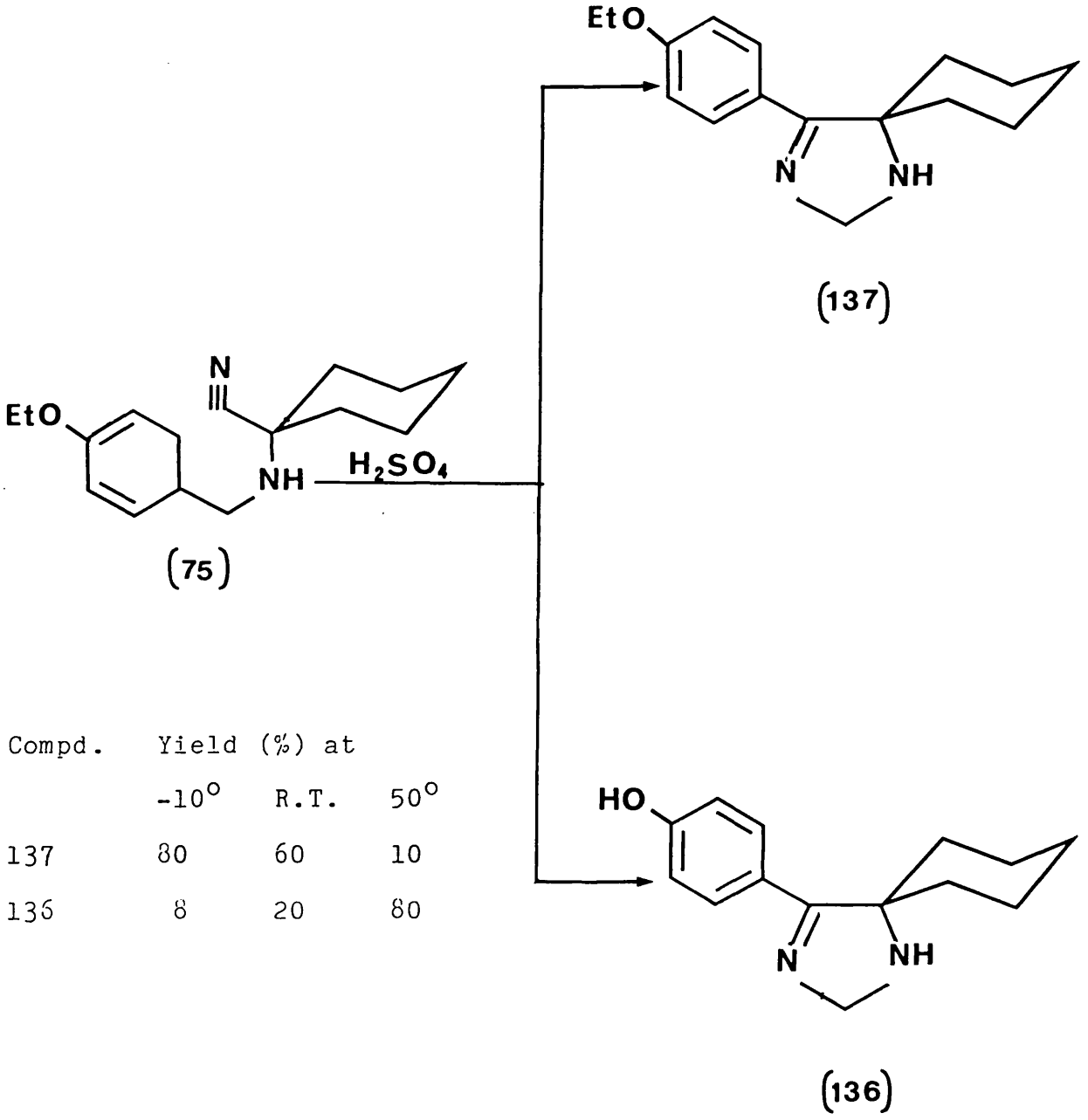
Compd.	Yield (%) at		
	-10^{o}	R.T.	50^{o}
135	87	82	70
136	2	6	20

Scheme 68

Similarly the cyclisation of the 1-(4-ethoxybenzyl-amino) cyclohexane carbonitrile (75) gave a single alkoxy imidazoline (137), whose ^{1}H n.m.r. spectrum differed from the methoxy analogue by the presence of a quartet (δ4.12-3.92 ppm) and triplet (δ1.44-1.28 ppm, J = 7 Hz), characteristic for an ethoxyl group. Again a single phenolic product was also obtained from this reaction, whose melting point and spectroscopic data revealed the product to be the hydroxy imidazoline (126).

However, the yields of phenolic product obtained from this cyclisation (scheme 69) are significantly higher than those obtained from cyclisation of the aminonitrile (74). For example, cyclisation at 50^{o} gave 20% yeild of phenolic product (from aminonitrile 74) compared with an 82% yield from the ethoxybenzylaminonitrile (75). This again is a reflection of the lability of the ethoxy group at the higher temperature.

As expected, no isoquinolinones were isolated since the iminium ion lacks the C3-alkoxy substituent necessary for Pictet-Spengler cyclisation.

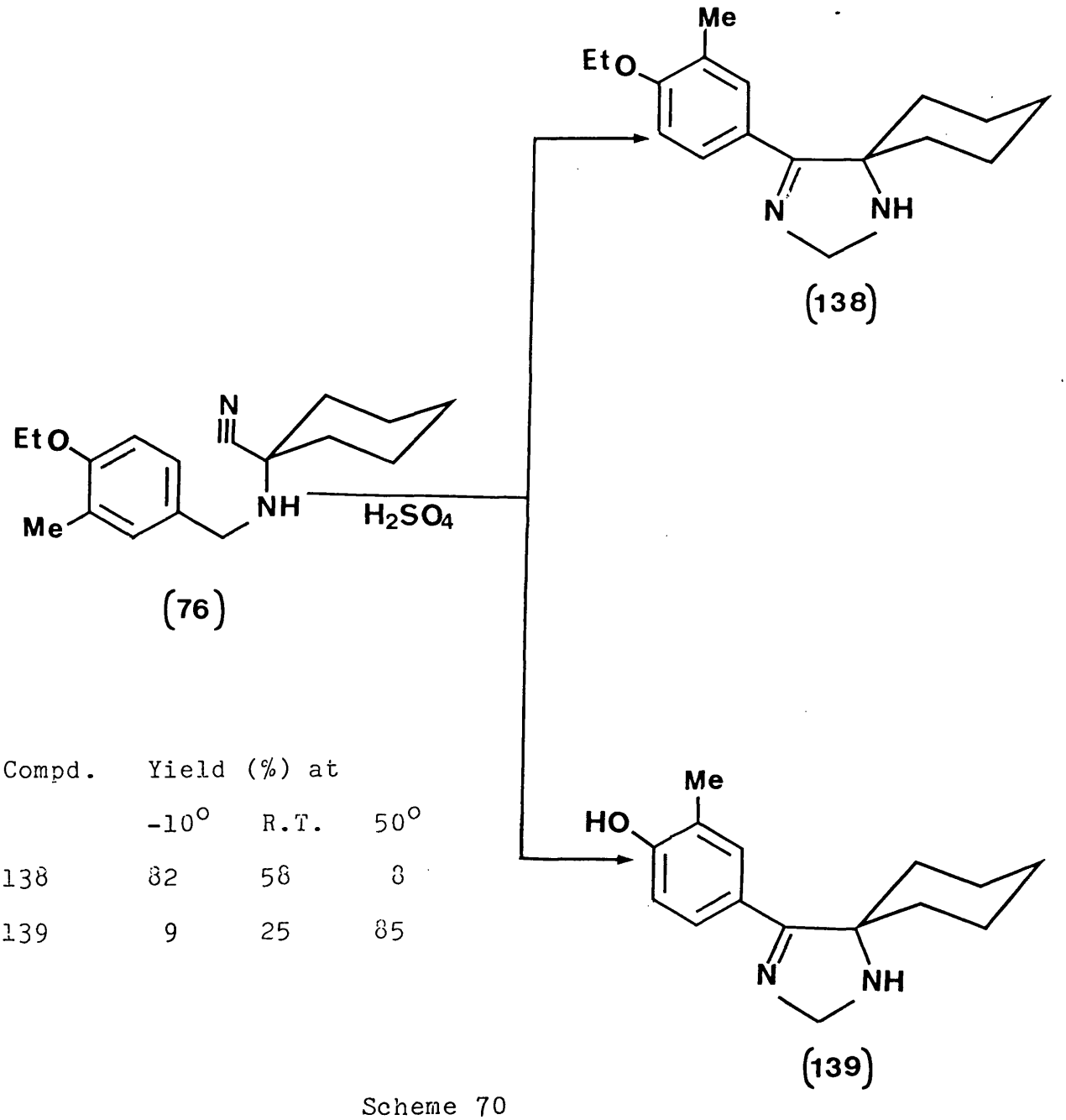


Compd.	Yield (%) at		
	-10^{o}	R.T.	50^{o}
137	80	60	10
136	8	20	80

Scheme 69

2.8.5 Cyclisation of 1-(4-ethoxy-3-methoxybenzyl-amino) cyclohexane carbonitrile (76)

Cyclisation of the aminonitrile (76) resulted in 3-imidazolines (138 and 139). The yields of which were temperature dependent (scheme 70).



Compd.	Yield (%) at		
	-10°	R.T.	50°
138	82	58	8
139	9	25	85

Scheme 70

The yields of these imidazolines (138 and 139) were virtually identical to their analogues (136 and 137) at each temperature of the cyclisation, clearly indicating that C3 substituent have no influence on the O-dealkylation of the C4 substituent. The influence of an additional alkyl substituent at C5 has yet to be investigated.

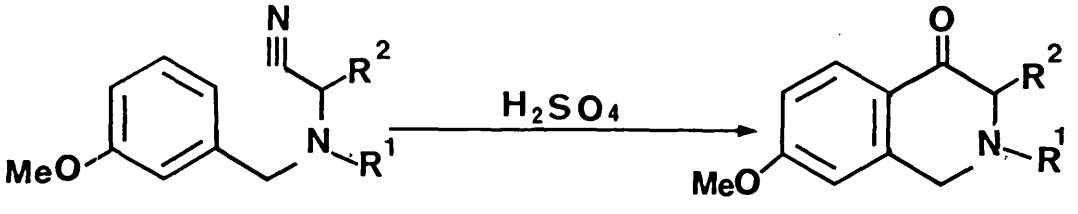
The ^{1}H n.m.r. spectrum (table 24, page 218) of the 3-imidazoline (138) exhibited a complex multiplet, due to the three aromatic protons between δ7.58 and 6.69 ppm. The methylene protons resonated at δ 4.72 ppm, while the ethoxyl group gave rise to a low field quartet (δ4.2-3.89 ppm) and a high field triplet (δ 1.46-1.32 ppm) with a coupling constant of 8 Hz. Singlets due to the methyl group and a deuterable proton of the secondary amine occurred at δ 2.25 and 1.9 ppm respectively. The ten protons of the cyclohexyl group resonated between δ 1.80-1.52 ppm.

The ^{1}H n.m.r. spectrum (table 24, page 218) of the phenolic imidazoline (139) exhibited a similar pattern to the alkoxy-imidazoline (138) except for the absence of signals due to an ethoxy group. Infra-red and mass spectra were unambiguous.

2.8.6 Cyclisation of 1-(3-methoxybenzylamino) cyclohexane carbonitrile (77) and 1-(2--ethoxybenzylamino) cyclohexane carbonitrile (78)

Cyclisation of aminonitrile (77) has been reported[59] to be unsuccessful at R.T. and 50°, which may be due to sulphonation of the ring. In view of the ease with which cyclisation via a spiro-intermediate occurs at -10°, it was hoped that these milder conditions would enable a successful classical cyclisation without sulphonation to be achieved. This was not the case however, all attempts to cyclise the 3-methoxyaminonitrile (77) at -10° failed. No material was recovered.

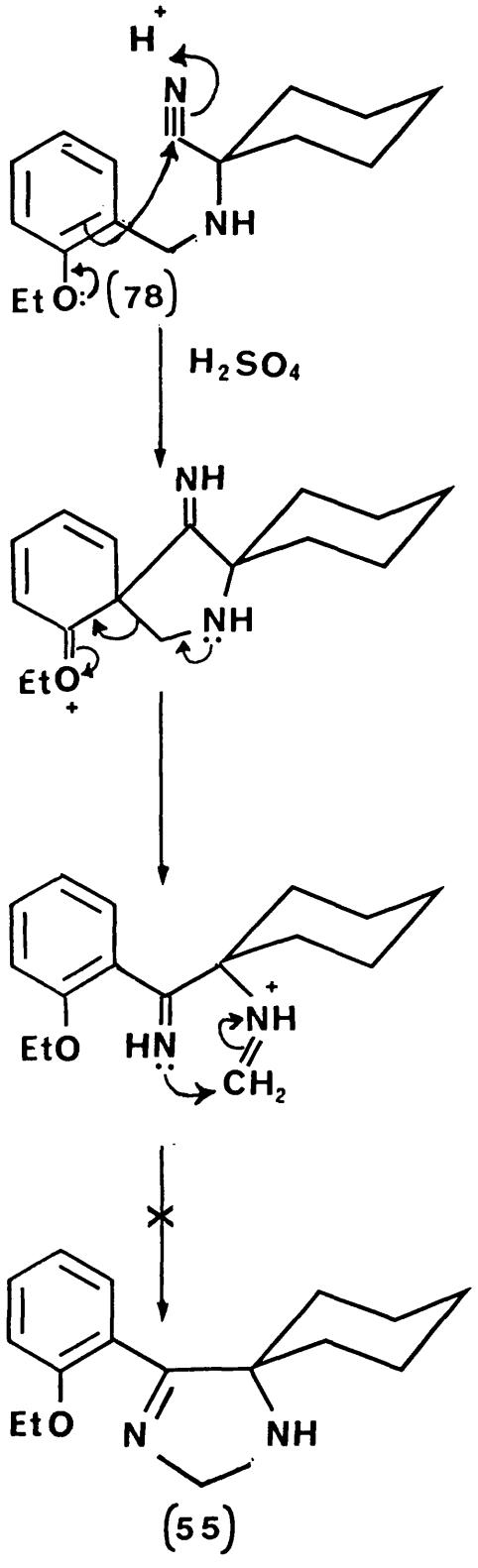
This failure cannot be explained because two 3-methoxybenzylaminonitriles (53) have been reported to give the 7-methoxyisoquinolinones (54) in moderate yields[64,68].



(53) (54)

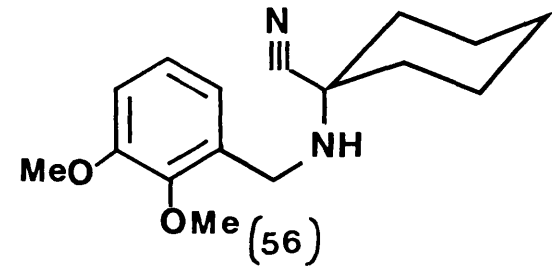
a. $R^1 = R^2 = H$
b. $R^1 = Me$; $R^2 = Ph$

Similarly cyclisation of aminonitrile (78) using concentrated sulphuric acid to yield the 3-imidazoline (55) was also fruitless (scheme 71), again neither alkoxy nor phenolic products were obtained.

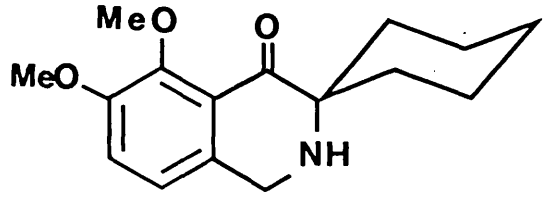


Scheme 71

Contrary to this finding cyclisation of aminonitrile (56) has been reported[59] to proceed via a spiro-intermediate to yield 5,6-dimethoxyisoquinolinone (57) in 5% yield.



(56)



(57)

It would appear that attack ortho to an alkoxy substituent to yield the spiro-intermediate is sterically unfavoured.

2.9.0 Reinvestigation of the cyclisation of 3,4-dimethoxybenzylglycine esters

The cyclisation of benzylglycine esters discussed in the introductory section (page 20) is carried out under similar conditions to the aminonitriles cyclisation, therefore, a similar pathway may operate.

The present work was undertaken to establish whether such a mechanism does exist in cyclisation of the glycine ethyl esters.

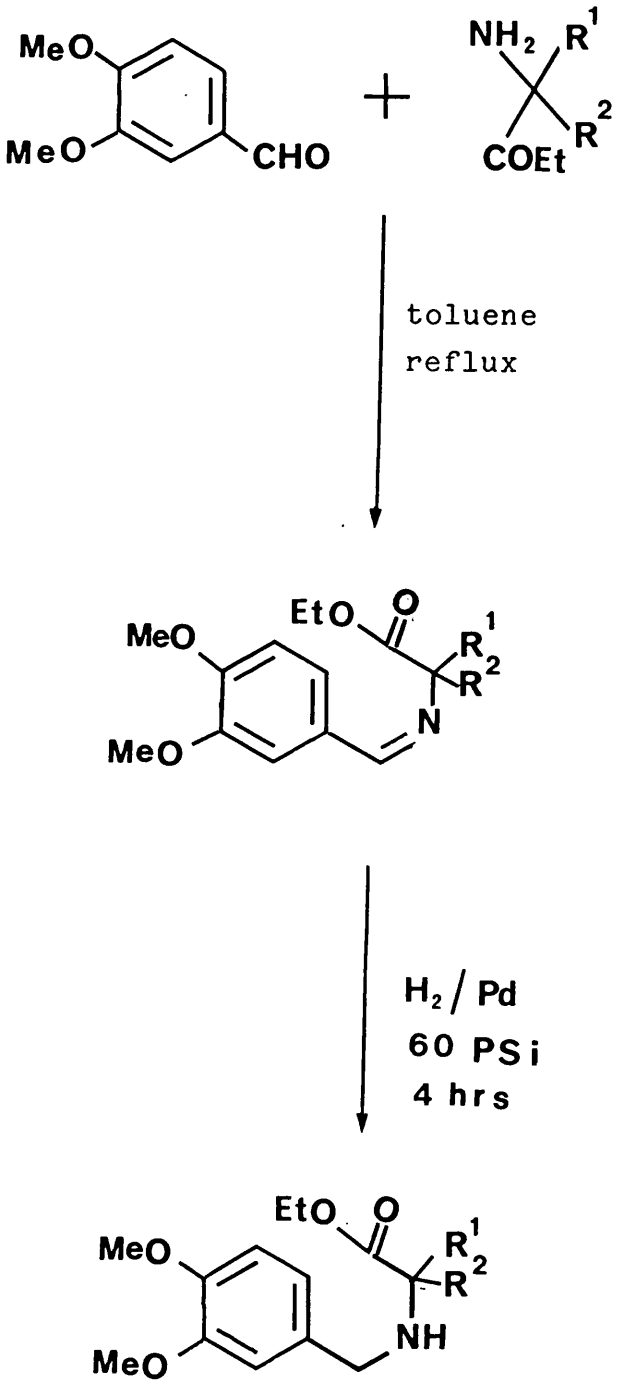
2.9.1 Preparation of benzylglycine ethyl esters

The compounds 3,4-dimethoxybenzyl-N-benzylglycine ethyl ester (140) and 3,4-dimethoxybenzylglycine ethyl ester (141) were prepared by the method of Grethe and co-workers[48].

However, the benzylglycine ethyl esters (142 and 143) were prepared by a modified procedure (scheme 72).

The spectroscopic data (table 27, page 226) and the melting point of N-benzylglycine ethyl ester (140) were in accord with published work[48].

The structures of glycine esters (141-143) were confirmed from their spectroscopic data (table 27, page 226).



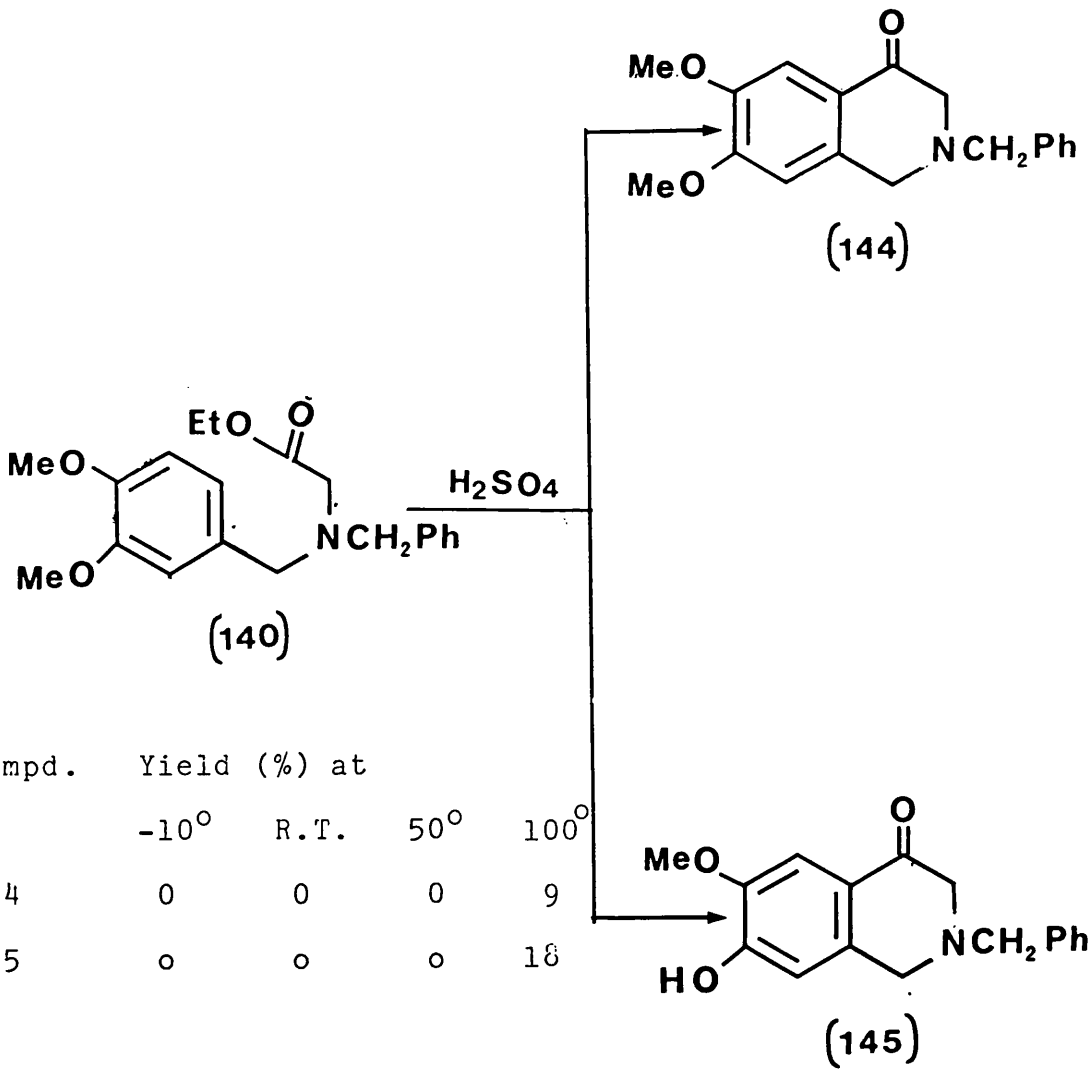
142 $R^1 = R^2 = Me$

143 $R^1 = R^2 = -CH_2(CH_2)_3CH_2-$

Scheme 72

2.9.2 Cyclisation of benzylglycine ethyl esters

It has been reported[48] that cyclisation of 3,4-dimethoxybenzyl-N-benzylglycine ethyl ester (140) in 70-90% sulphuric acid at 100° gave 2,3-dihydro-6,7-dimethoxy--4(1H)-isoquinolinone hydrochloride (144) in 10% yield. There was no report of the phenolic product being isolated. Subsequently in the present investigation not only the dimethoxyisoquinolinone (144) was isolated but also 2,3-dihydro-7-hydroxy-6-methoxy-4(1H)-isoquinolinone (145) in yield of 18% (scheme 73).



Compd.	Yield (%) at			
	-10°	R.T.	50°	100°
144	0	0	0	9
145	o	o	o	18

Scheme 73

The spectroscopic data (tables 29 and 30 pages 228,229) of the dimethoxyisoquinolinone (144) were consistent with reported structural assignment . Orientation of the hydroxy substituent in the phenolic product (145) was established by ultra-violet spectroscopy and ^{1}H n.m.r. (including NaOD shift).

Thus the ^{1}H n.m.r. spectrum exhibited a deuterable broad singlet (due to the hydroxy group) between δ 10.40 and 9.80 ppm and singlets resulting from C5 and C8 protons at δ 7.36 and 6.7 ppm respectively. However, on addition of NaOD in D_2O both these signals are shifted upfield to δ 7.16 and 6.22 representing an upfield shift of 20 and 44 Hz respectively, indicating the location of the hydroxyl group at C7.

The rest of the spectrum was identical to its dimethoxy isomer (144) apart from only one methoxyl signal. Infra-red and mass spectra were unambiguous.

In order to achieve a reasonable yield of the dimethoxyisoquinolinone (144), cyclisation under identical temperatures to those used for the benzylaminonitriles (i.e. -10° R.T. and 50°) was carried out. Unfortunatly no product could be isolated at these lower temperatures. Both 80% and concentrated sulphuric acid were used. This is probably due to the fact that at these temperatures hydrolysis of the esters results, yielding the benzylglycine which, has unfavourable solubility characteristics.

The cyclisation of glycine ethyl esters (141-143) under the above conditions was also unsuccessful. This

failure (especially at conditions identical to cyclisation of glycine ethyl ester, 140) cannot be explained.

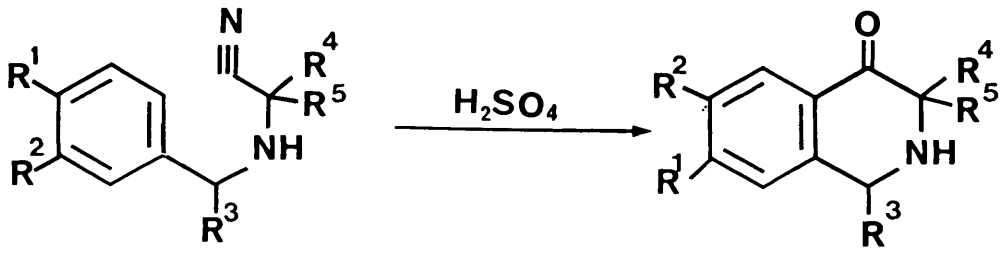
In view of this lack of success, it did not appear worthwhile preparing the corresponding ethoxymethoxybenzylaminoglycine esters in order to establish whether these esters, like the nitriles, cyclised via a spiro-intermediate.

PART III

SUGGESTIONS FOR FURTHER WORK

1. Synthesis of 1-substituted isoquinolinones

There have been numerous publications relating to the cyclisation of benzylaminonitriles, but none refer to the synthesis of 1-substituted isoquinolinones. In view of the flexibility of the Strecker nitrile synthesis, the preparation and cyclisation of benzylaminonitriles bearing a variety of benzylic-substituent groups should be carried out.

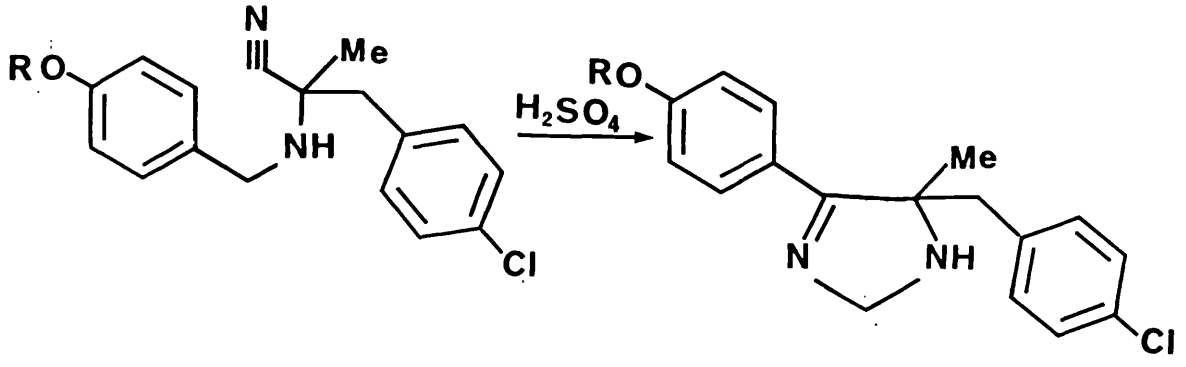


2. Synthesis of 5-benzyl substituted imidazolines

It was previously reported that the 2(4-methoxybenzyl-amino)2-benzylpropionitrile gave the 3(4-methoxybenzoyl)3--methyl-1,2,3,4-tetrahydroisoquinolinone.

The analogous 4-ethoxybenzylaminonitrile (73, page 116) also yielded no imidazoline and gave the 3(4-ethoxybenzoyl)-3--methyl-1,2,3,4-tetrahydroisoquinoline (112) and its phenolic analoue. In neither case is any 3-imidazoline produced.

However, if the aromatic ring of the benzyl substituent is deactivated (for example by possessing a chloro-substituent) then the pathway to this alternative nucleophile is blocked and will allow the addition of the imine to the iminium ion, with the formation of 5-benzyl substituted imidazoline, a class of compound yet to be investigated.

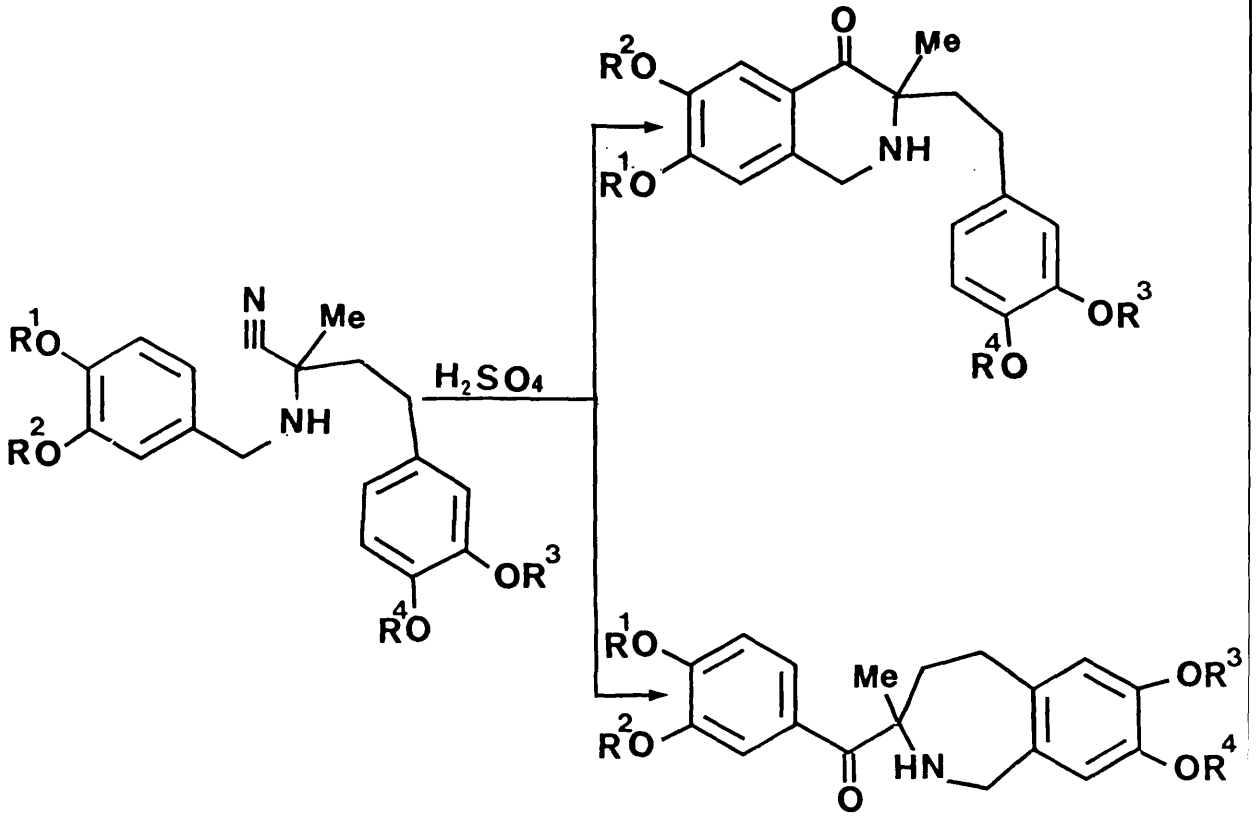


3. Cyclisation of benzylaminonitriles with phenethyl substituent

Present work on the dialkoxy benzylaminonitriles with a phenethyl substituent indicated that cyclisation proceeds exclusively via the spiro-intermediate to form 6,7-disubstituted isoquinolinones. No 2-benzazepine could be detected.

The possibility of enhancing the formation of the 2-benzazepine should be explored by a study of the cyclisation of aminonitriles where the phenethyl substituent possesses electron donating groups in the aromatic ring.

As for the benzyl analogues described in this thesis, careful separation of crude reaction mixtures should enable an assessment to be made of the competition between isoquinolinone and 2-benzazepine formation.



PART IV

EXPERIMENTAL

Instrumental Methods

Infra-red spectra were recorded on a unicom S.P. 1025 spectrophotometer as potassium bromide discs or liquid films, for solids and liquids respectively.
^{1}H.n.m.r. spectra were recorded on a Jeol JNM-PS 100 MHz at the School of Chemistry, University of Bath.

Chemical shifts were measured in ppm dowfield from tetramethylsilane as internal standard.

Ultra-violet spectra were recorded on a Perkin - Elmer 550S photometer. Mass spectra were recorded at the School of Chemistry, University of Bath using V.G. 7070E, mass spectrometer.

Elemental analyses were carried out by the Butterworth Laboratories Limited, Teddington.

Melting points were taken on a Gallenkamp melting point apparatus and are corrected.

The following abbreviations have been used throughout the text: I.r = infra-red, ^{1}H n.m.r. = proton nuclear magnetic resonance, $CDCl_3$ = trideuterochloroform, DMSO = dimethylsulphoxide, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, m.p. = melting point, b.p. = boiling point, u.v. = ultra-violet, t.l.c. = thin layer chromatography.

4-ethoxy-3-methoxybenzaldehyde

To a solution of vanillin (30.4 g, 0.2 mol) in 95% ethanol (120 ml) was added, potassium hydroxide (12.3 g, 0.22 mol) in 95% ethanol (120 ml) and the mixture gently

refluxed. Iodoethane (40.6 g, 0.26 mol) was added dropwise over a period of 0.5 hour.

The reaction mixture was refluxed for further 2.5 hours and poured onto crushed ice (500 g) followed by basification with 5M sodium hydroxide (250 ml). The mixture was stirred for 0.5 hour and the product isolated by filtration.

The crude product was thoroughly washed with water and dried to give white needles of 4-ethoxy-3-methoxybenzaldehyde (27.0 g, 75%) m.p. 63-64° (lit[101] 64-65°).

3-ethoxy-4-methoxybenzaldehyde

By the above procedure using isovanillin as starting material, the product was obtained as white needles of 3-ethoxy-4-methoxybenzaldehyde (25.5 g, 71%) m.p. 50-51° (lit[102] 50-51°).

4-hydroxy-3-methylbenzaldehyde

The preparation of 4-hydroxy-3-methylbenzaldehyde was carried out as described by Smith's method[100].

Thus a mixture of O-cresol (54 g, 0.5 mol), hexamethylene-tetramine (70 g, 0.5 mol) and trifluoroacetic acid (900 ml) was heated under reflux (83-90°) for 12 hours, the product was concentrated under reduced pressure and poured over two litres of iced water.

The resulted mixture was stirred for 0.5 hour, made basic with sodium carbonate and extracted with ether (5 x 200 ml). Evaporation of the ether solution left a yellow oil of 4-hydroxy-3-methylbenzaldehyde (50 g, 72%)

which was used in the next step without further purification.

4-ethoxy-3-methylbenzaldehyde

To a solution of 4-hydroxy-3-methylbenzaldehyde (47.95 g, 0.35 mol) in 95% ethanol (200 ml) was added potassium hydroxide (22.4 g, 0.4 mol) in 95% ethanol (200 ml) and the mixture was gently refluxed.

Iodoethane (70.2 g, 0.45 mol) was added dropwise over a period of 0.5 hour. The resulting yellow solution was refluxed for further 2.5 hours and then cooled to room temperature, poured onto crushed ice (400 g) and basified with 5M sodium hydroxide (250 ml). The mixture was stirred for 0.5 hour and the product was extracted with chloroform (3 x 200 ml), washed with water and dried with magnesium sulphate.

Removal of solvent under reduced pressure furnished red coloured oil (44 g), which was distilled under vacuum collecting the yellow oil of 4-ethoxy-3-methylbenzaldehyde (38 g, 66%) b.p. 129-130° 6 mm Hg (lit[103] 120-127° 4-5 mm Hg).

4-trideuteromethoxy-3-methoxybenzaldehyde

The method used was an adaptation of that employed by Vyas and Shah[97] with slight modification.

To a solution of vanillin (30 g 0.197 mol) and acetone (300 ml) was added anhydrous potassium carbonate (28 g, 0.10 mol), followed by Iodotrideuteratedmethane (42 g, 0.147 mol). The mixture was allowed to reflux on water bath at 60-70° for 6 hours. Acetone was removed under reduced pressure and the residue was poured onto iced water and basified with 5M sodium hydroxide. The resulting mixture was stirred for 0.5 hour and then extracted with chloroform (3 x 100 ml), washed the combined organic extracts with water, dried with magnesium sulphate and filtered.

The removal of solvent under reduced pressure gave a yellow oil, which leaving at room temperature for two hours, resulted in crystalline solid. The crystallisation of residue from petroleum-ether (60-80°) furnished white needles of 4-trideuteromethoxy-3-methoxybenzaldehyde (23 g, 68%) m.p. 52-59°.

3-trideuteromethoxy-4-methoxybenzaldehyde

Prepared by the above procedure using isovanillin as starting material, the product was obtained as cream coloured needles of 3-trideuteromethoxy-4-methoxybenzaldehyde (22 g, 66%), m.p. 55-56°).

General method for the preparation of Alkoxybenzylamines

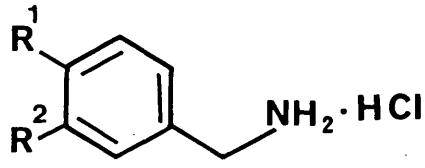
The aldehyde (0.25 mol), hydroxylamine hydrochloride (0.275 mol), sodium acetate (0.4 mol) were dissolved in 70% ethanol (450 ml) and refluxed for 6 hours.

The reaction mixture was cooled and 2M sodium hydroxide (450 ml) added. Raney alloy (35 g) was added in portions to the stirred solution and stirring was continued until the evolution of hydrogen ceased. The catalyst was removed by filtration, the filterate was extracted with chloroform (3 x 200 ml) and the combined extracts were washed with water, dried with anhydrous magnesium sulphate and filtered.

The solvent was removed under reduced pressure to give the amine (tablel), which was used in the next step without further purification.

Table 1

Benzylamine derivatives



R^1	R^2	Yield (%)	m.p. (°C)
CH_3O	CH_3O	76	256-257 (lit[104] 257-258)
CH_3O	CH_3CH_2O	66	229-230 (lit[88] 228-230)
CH_3CH_2O	CH_3O	77	228-229 (lit[101] 229)
CH_3O	H	73	228-229 (lit[105] 230-231)
CH_3CH_2O	H	78	228-229 (lit[106] 231-233)
CH_3CH_2O	CH_3	71	238-239
CD_3O	CH_3O	71	256-257
CH_3O	CD_3O	66	257-258
H	CH_3O	69	165-166 (lit[48] 166-167)

General method for the preparation of Benzyloxybenzaldehyde

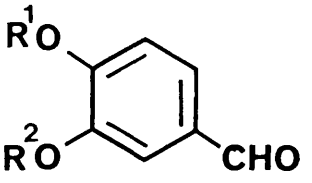
The aldehyde (0.33 mol), potassium carbonate (o.23 mol) and potassium iodide (0.032 mol) were dispersed in a mixture of 95% ethanol (100 ml) and water (30 ml).

Benzylchloride (0.43 mol) was added and the reaction mixture was refluxed for 6.5 hours. Triethylamine (0.095 mol) was added and the mixture was refluxed for further 0.25 hour.

The solution was cooled and poured onto crushed ice (200 g) followed by basification with 1.0M sodium hydroxide (300 ml). The mixture was stirred for 0.5 hour and the product collected by filtration, thoroughly washed with water and dried. Recrystallization from petroleum-ether (69-80°) /ethylacetate 1:1 gave the appropriate benzyloxy-benzaldehyde. (Table 2)

Table 2

Benzaldehyde derivatives



R^1	R^2	Yield (%)	m.p. (°C)
$C_6H_5CH_2$	CH_3	75	60-61 (lit[107] 60-62)
CH_3	$C_6H_5CH_2$	72	45-46 (lit[15] 44-45)
C_2H_5	$C_6H_5CH_2$	74	76-77 (lit[108] 77-78)
$C_6H_5CH_2$	C_2H_5	77	61-62 (lit[109] 60-62)

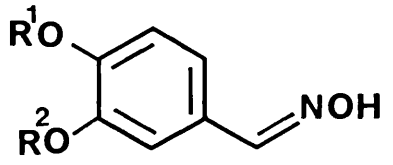
General method for the preparation of Benzyloxybenzaldoximes

The aldehyde (0.188 mol), hydroxylamine hydrochloride (0.21 mol) and sodium acetate (0.3 mol) were dissolved in 70% ethanol (340 ml) and refluxed for 6 hours.

The resulting mixture was cooled and ethanol was removed under reduced pressure. The residue was poured into water (300 ml), and the precipated solid was filtered off to give the oxime, which was recrystallized from petroleum-ether (60-80°) to yield white needles of appropriate oxime. (Table 3)

Table 3

Benzaldoximes derivatives



R^1	R^2	Yield (%)	m.p. (°C)
$C_6H_5CH_2$	CH_3	83	61-62 (lit[110] 60-61
CH_3	$C_6H_5CH_2$	79	94-95 (lit[111] 96-97)
$C_6H_5CH_2$	C_2H_5	75	101-102
C_2H_5	$C_6H_5CH_2$	79	108-109

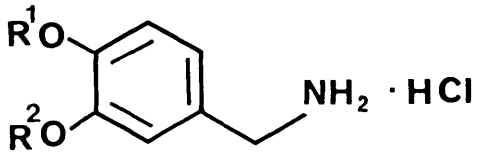
General method for the preparation of Hydroxybenzylamines

A solution of benzaldoxime (0.116 mol) in methanol (250 ml) was hydrogenated over 5% palladium on charcoal (2.5 g) at room temperature and 60 p.s.i. until the hydrogen uptake ceased (4 hours). The catalyst was removed by filtration and washed thoroughly with warm methanol.

The combined filterate and washings were evaporated under reduced pressure to give yellow oil of appropriate hydroxybenzylamines (table 4), which were used for the preparation of aminonitriles without further purification.

Table 4

Benzylamine derivatives



R^1	R^2	Yield (%)	m.p. (°C)
H	CH_3	88	226-228 (lit[112] 227)
CH_3	H	90	187-188 (lit[112] 185-186)
H	C_2H_5	86	220-221 (lit[113] 222-223)
C_2H_5	H	88	225-226

4.1 General method for the preparation of Benzylaminoacetonitriles

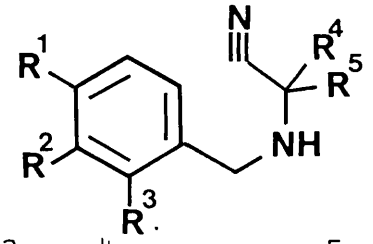
The benzylamine (0.15 ml) was suspended in water (100 ml) and made just acid with hydroxhloric acid. The appropriate carbonyl compound (0.15 mol) and 95% ethanol (100 ml) was added.

The resulting mixture was stirred until dissolved, a solution of potassium cyanide (0.23 mol) in water (100 ml) was added dropwise over a period of 0.5 hour and the reaction mixture left stirring overnight.

The product was filtered or extracted with chloroform (4 x 100 ml), washed thoroughly with water, dried and recrystallised to give the required nitrile. (Table 5)

Table 5

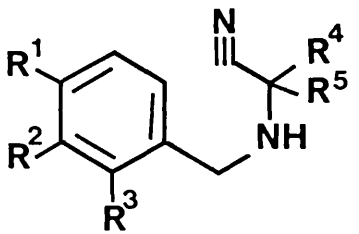
Benzylaminoacetonitriles



Compound	R^1	R^2	R^3	R^4 R^5	Yield (%)	m.p. (°C)	Recrystallization solvent pet-ether (60-80°)/ethylacetate
58	CH_3O	CH_3O	H	$-CH_2(CH_2)_3CH_2-$	88	87 (lit[51] 88)	1:0
59	CH_3CH_2O	CH_3O	H	$-CH_2(CH_2)_3CH_2-$	88	83-83 (lit[88] 83)	1:0
60	CH_3O	CH_3CH_2O	H	$-CH_2(CH_2)_3CH_2-$	86	83 (lit[88] 83)	1:0
61	HO	CH_3O	H	$-CH_2(CH_2)_3CH_2-$	78	82-83	1:1
62	CH_3O	HO	H	$-CH_2(CH_2)_3CH_2-$	80	113-114	1:1
63	HO	CH_3CH_2O	H	$-CH_2(CH_2)_3CH_2-$	86	77-78	1:1
64	CH_3CH_2O	Ho	H	$-CH_2(CH_2)_3CH_2-$	84	70-71	1:1

Table 5 (continued)

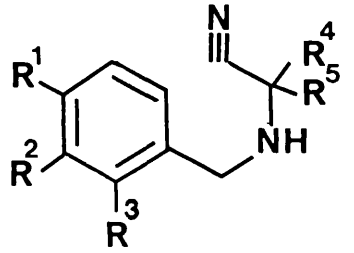
Benzylaminoacetonitriles



Compound	R^1	R^2	R^3	R^4	R^5	Yield (%)	m.p. (^oC)	Recrystallisation solvent pet ether (60-80^o)/ethylacetate
65	CD_3O	CH_3O	H	$-CH_2(CH_3)_3CH_2-$		86	83-84	1:0
66	CH_3O	CD_3O	H	$-CH_2(CH_2)_3CH_2-$		85	87-88	1:0
67	CH_3O	CH_3O	H	CH_3	$CH_2C_6H_5$	82	81-82 (lit[65] 82)	1:0
68	CH_3CH_2O	CH_3O	H	CH_3	$CH_2C_6H_5$	89	52-53	3:1
69	CH_3O	CH_3CH_2O	H	CH_3	$CH_2C_6H_5$	88	54-55	1:1
70	CH_3O	CH_3O	H	CH_3	$CH_2CH_2C_6H_5$	87	65-66	2:1
71	CH_3CH_2O	CH_3O	H	CH_3	$CH_2CH_2C_6H_5$	90	47-48	2:1

Table 5 (continued)

Benzylaminoacetonitriles



Compound	R^1	R^2	R^3	R^4	R^5	Yield (%)	m.p. (°C)	Recrystallisation solvent pet-ether (60-80°)/ethylacetate
72	CH_3O	CH_3CH_2O	H	CH_3	$CH_2CH_2C_6H_5$	85	49-50	2:1
73	CH_3CH_2O	H	H	CH_3	$CH_2C_6H_5$	88	61-62	3:1
74	CH_3O	H	H	$-CH_2(CH_2)_3CH_2-$		86	62 (lit[66] 82)	1:0
75	CH_3CH_2O	H	H	$-CH_2(CH_2)_3CH_2-$		90	35-36	3:1
76	CH_3CH_2O	CH_3	H	$-CH_2(CH_2)_3CH_2-$		85	54-55	2:1
77	H	CH_3O	H	$-CH_2(CH_2)_3CH_2-$		83	Oil	—
78	H	H	OEt	$-CH_2(CH_2)_3CH_2-$		75	38-39	3:1

Table 6

Elemental analysis of Benzylaminoacetonitriles

Compound	Formula	Found %			Required %		
		C	H	N	C	H	N
58	$C_{16}H_{22}N_2O_2$	Previously characterised [51]					
59	$C_{17}H_{24}N_2O_2$	Previously characterised [88]					
60	$C_{17}H_{24}N_2O_2$	Previously characterised [88]					
61	$C_{15}H_{20}N_2O_2$	69.60	7.87	10.98	69.20	7.74	10.76
62	$C_{15}H_{20}N_2O_2$	69.48	7.84	11.06	69.20	7.74	10.76
63	$C_{16}H_{22}N_2O_2$	69.87	8.08	10.06	70.04	8.08	10.21
64	$C_{16}H_{22}N_2O_2$	69.89	8.09	9.92	70.04	8.08	10.21
65	$C_{16}H_{19}D_3N_2O_2$						
66	$C_{16}H_{19}D_3N_2O_2$						
67	$C_{19}H_{22}N_2O_2$	Previously characterised [65]					
68	$C_{20}H_{24}N_2O_2$	74.58	7.58	8.90	74.40	7.46	8.63

Table 6 (continued)

Elemental analysis of Benzylaminoacetonitriles

Compound	Formula	Found %			Required %		
		C	H	N	C	H	N
69	$C_{20}H_{24}N_2O_2$	74.28	7.71	8.91	74.40	7.46	8.63
70	$C_{20}H_{24}N_2O_2$	73.89	7.57	8.87	74.05	7.46	8.63
71	$C_{21}H_{26}N_2O_2$	74.58	7.76	8.16	74.52	7.74	8.28
72	$C_{21}H_{26}N_2O_2$	74.65	7.82	8.28	74.52	7.74	8.28
73	$C_{19}H_{22}N_2O_2$	77.76	7.61	9.51	77.52	7.53	9.52
74	$C_{15}H_{20}N_2O$	Previously characterised[66]					
75	$C_{16}H_{22}N_2O$	74.44	8.73	10.83	74.38	8.58	10.84
76	$C_{17}H_{24}N_2O$	75.01	8.95	10.39	74.96	8.88	10.28
77	$C_{15}H_{20}N_2O$	Previously characterised[59]					
78	$C_{16}H_{22}N_2)$	74.41	8.55	10.87	74.38	8.58	10.84

Table 7

Spectroscopic data for benzylaminoacetonitriles

Compound	ν_{max} /cm^{-1} NH(OH)	C≡N	δ_H (100 MHz; solvent $CDCl_3$; standard TMS)
58	3455	2165	6.9-6.8 (3H,m,C_6H_3), 3.85 (6H,2s,2 x OCH_3), 3.80 (2H,s,Ar$\underline{CH_2}$-), 2.0-1.4 (11*H,m,C_5H_{10}+NH)
59	3450	2160	7.0-6.8 (3H,m,C_6H_3), 4.2-3.8 (2H,q,O$\underline{CH_2}CH_3$,J=8Hz), 3.82 (3H,s,OCH_3), 3.8 (2H,s,Ar$\underline{CH_2}$-), 1.48-1.38 (3H,t,OCH_2CH_3, J=8Hz), 1.9-1.5 (11*H,m,C_5H_{10}+NH)
60	3350	2160	7.0-6.84 (3H,m,C_6H_3), 4.2-3.8 (2H,q,O$\underline{CH_2}CH_3$, J=8Hz), 3.82 (3,s,OCH_3), 3.8 (2H,s,$ArCH_2$), 1.41 (3H,t,OCH_2CH_3, J=8Hz), 2.0-1.5 (11*H,m,C_5H_{10}+NH)
61	3340 (3495)	2250	8.7 (1H,s,OH)$^{\Phi}$, 6.9-6.7 (3H,m,C_6H_3). 3.79 (3H,s,OCH_3), 3.7 (2H,s,Ar$\underline{CH_2}$- 2.7 (1H,broad s,NH)$^{\Phi}$, 2.0-1.2 (10H,m,C_5H_{10})
62	3330 (3500)	2245	8.78 (1H,s,OH)$^{\Phi}$, 6.9-6.75 (3H,m,C_6H_3), 3.7 (3H,s,OCH_3), 3.6 (2H,s,Ar$\underline{CH_2}$-), 2.73 (1H,s,NH)$^{\Phi}$, 1.96-1.2 (10H,m,C_5H_{10}).
63	3320 (3480)	2240	7.02-6.90 (3H,m,C_6H_3), 4.2-3.95 (2H,q,O$\underline{CH_2}CH_3$, J=8Hz), 3.8 (2H,s,Ar$\underline{CH_2}$-), 2.08-1.52 (11*,m,C_5H_{10}+NH), 1.47-1.35 (3H,t,$OCH_2\underline{CH_3}$, J=8Hz
64	3325 (3475)	2245	7.02-6.85 (3H,m,C_6H_3), 4.20-4.00 (2H,q,OCH_2CH_3, J=8Hz), 3.0 (2H,s,Ar$\underline{CH_2}$), 2.00-1.55 (11*H,m,C_5H_{10}+NH), 1.48-1.34 (3H,t,$OCH_2\underline{CH_3}$, J=8Hz).

Table 7 (continued)

Spectroscopic data for benzylaminoacetonitriles

Compound	ν_{max} /cm^{-1} NH(OH)	C≡N	δ_H (100 MHz; solvent $CDCl_3$; standard TMS)
65	3450	2230	7.0-6.7 (3H,m,C_6H_3), 3.87 (3H,s,OCH_3), 3.80 (2H,s,Ar$\underline{CH_2}$-), 2.00-1.40 (11*H,m,C_5H_{10}+NH).
66	3455	2235	6.95-6.80 (3H,m,C_6H_3) 3.90 (3H,s,OCH_3), 3.85 (2H,s,Ar$\underline{CH_2}$-), 2.20-1.40 (11*H,m,C_5H_{10}+NH).
67	3300	2240	7.30-725 (5H,m,-$CH_2\underline{Ar}$), 6.85-672 (3H,m,C_6H_3), 3.78 (8H,2s,2 x OCH_3+ Ar$\underline{CH_2}$ -N-), 2.90 (2H,s,-CH_2Ar), 1.60 (1H,broad s,NH)$^{\Phi}$, 1.40 (3H,s,-CH_3).
68	3330	2210	7.38-7.20 (5H,m,$\underline{Ar}CH_2$-), 6.85-6.75 (3H,m,C_6H_3), 4.12-3.92 (2H,q,$O\underline{CH_2}CH_3$, J=7Hz), 3.80 (5H,s,OCH_3+Ar-$\underline{CH_2}$-NH-), 2.98 (2H,s,-$\underline{CH_2}$Ar) 1.58 (1H,broad s,NH)$^{\Phi}$, 1.46-1.28 (3H,t,$OCH_2\underline{CH_3}$, J=7Hz), 1.42 (3H,s,-CH_3).
69	3335	2220	7.40-7.20 (5H,m,-$CH_2\underline{Ar}$), 6.90-6.75 (3H,m,C_6H_3), 4.14-3.94 (2H,q,$O\underline{CH_2}CH_3$, J=8Hz), 3.80 (5H,s,OCH_3+Ar-$\underline{CH_2}$-NH-), 2.96 (2H,s,-$\underline{CH_2}$Ar), 2.00 (1H,broad s,NH)$^{\Phi}$, 1.48-1.34 (3H,t,$OCH_2\underline{CH_3}$, J=8Hz), 1.40 (3H,s,CH_3).
70	3355	2215	7.25-7.04 (5H,m,-$CH_2CH_2\underline{Ar}$), 6.90-6.70 (3H,m,C_6H_3), 3.80 (8H,s,2 x OCH_3+ Ar-$\underline{CH_2}$-NH-), 2.90-2.64 (2H,m,-$CH_2\underline{CH_2}$Ar), 2.06-1.84 (2H,m,-$\underline{CH_2}CH_2$Ar), 1.60 (1H,s,NH)$^{\Phi}$, 1.48 (3H,s,CH_3).

Table 7 (continued)

Spectroscopic data for benzylaminoacetonitriles

Compound	ν_{max} /cm^{-1} NH(OH)	C≡N	δ_H (100 MHz; solvent $CDCl_3$; standard TMS)
71	3325	2210	7.30-7.00 (5H,m,-CH_2CH_2Ar), 6.90-6.72 (3H,m,C_6H_3), 4.10-3.90 (2H,q,OCH_2CH_3, J=8Hz), 3.80 (5H,s,OCH_3+ArCH_2-NH-), 2.90-2.64 (2H,m,-CH_2CH_2Ar), 2.06-1.85 (2H,m,-CH_2CH_2Ar), 1.56 (1H,s,NH)$^{\Phi}$, 1.49-1.18 (3H,t,OCH_2CH_3,J=8Hz), 1.48 (3H,s,CH_3).
72	3320	2210	7.32-7.02 (5H,m,-CH_2CH_2Ar), 6.90-6.70 (3H,m,C_6H_3), 4.10-3.88 (2H,q,OCH_2CH_3, J=8Hz), 3.81 (5H,s,OCH_3+Ar-CH_2-NH-), 2.88-2.68 (2H,m,-CH_2CH_2Ar), 2.08-1.88 (2H,m,-CH_2CH_2Ar), 1.58 (1H,s,NH)$^{\Phi}$, 1.49-1.15 (3H,t,OCH_2CH_3, J=8Hz) 1.48 (3H,s,CH_3).
73	3360	2250	7.32-7.25 (5H,m,-CH_2Ar), 7.22-6.40 (4H,AA^1XX^1,C_6H_4), 4.10-3.82 (2H,q,OCH_2CH_3, J=7Hz), 3.76 (2H,s,Ar-CH_2-NH-), 2.90 (2H,s,-CH_2-Ar), 1.52 (1H,s,NH)$^{\Phi}$, 1.36 (3H,s,CH_3), 1.40-1.24 (3H,t,OCH_2CH_3, J=7Hz).
74	3300	2240	7.30-6.70 (4H,AA^1XX^1,C_6H_4), 3.85 (3H,s,OCH_3), 3.80 (2H,s,ArCH_2-), 2.00-1.20 (11H*,m,C_5H_{10}+NH).
75	3350	2255	7.28-6.70 (4H,AA^1XX^1,C_6H_4), 4.04-3.84 (2H,q,OCH_2CH_3, J=8Hz), 3.8 (1H,s,NH)$^{\Phi}$, 3.72 (2H,s,-CH_2Ar), 2.00-1.46 (10H,m,C_5H_{10}), 1.40-1.22 (3H,t,OCH_2CH_3, J=8Hz).

Table 7 (continued)

Spectroscopic data for benzylaminoacetonitriles

Compound	ν_{max} /cm^{-1} NH(OH)	C≡N	δ_H (100 MHz; solvent $CDCl_3$; standard TMS)
76	3360	2250	7.12-6.60 (3H,m,C_6H_3), 4.4-3.84 (2H,q,$O\underline{CH_2}CH_3$,J=8Hz), 3.70 (2H,s,-$\underline{CH_2}$Ar), 2.20 (3H,s,-CH_3), 2.00-1.40 (11*H,m,C_5H_{10}+NH), 1.40-1.28 (3H,t,$OCH_2\underline{CH_3}$,J=8Hz).
77	3310	2245	7.3-6.7 (4H,m,C_6H_4), 3.90 (2H,s,-$\underline{CH_2}$Ar), 3.85 (3H,s,OCH_3) 2.0-1.25 (11*H,m,C_5H_{10}+NH).
78	3350	2240	7.30-6.72 (4H,m,C_6H_4), 4.08-3.92 (2H,q,$O\underline{CH_2}CH_3$,J=7Hz), 3.86 (2H,s,-$\underline{CH_2}$Ar), 2.00-1.48 (10H,m,C_5H_{10}), 1.88 (1H,s,NH)Φ, 1.48-1.28 (3H,t,$OCH_2\underline{CH_3}$J=7Hz).

* reduced to 10 after deuteration.

Φ disappeared after deuteration.

Table 8

Mass spectral fragmentation of benzylaminoacetonitriles. (electron impact)

Compound		Relative abundancies
58	m/z	274 ($M^{\ddagger}$0.29%), 247 (29.04), 151 (100), 136 (9.32), 121 (14.28)
59	m/z	228 ($M^{\ddagger}$,0.5%), 261 (21), 165 (100), 137 (76.01), 107 (3.21).
60	m/z	228 ($M^{\ddagger}$1.0%), 261 (11.02), (100), 137 (14.00), 107 (5.32).
61	m/z	260 ($M^{\ddagger}$0.81%), 223 (13.60), 137 (100), 122 (5.35), 97 (5.65).
62	m/z	260 ($M^{\ddagger}$0.75%), 233 (17.68), 137 (100), 122 (4.41), 97 (5.16).
63	m/z	274 ($M^{\ddagger}$1;10%), 247 (15.76), 151 (100), 123 (62.99), 122 (5.37), 97 (18.40).
64	m/z	274 ($M^{\ddagger}$11.18%), 247 (18.46), 151 (100), 123 (85.99), 122 (6.59), 97 (11.20).
65	m/z	277 ($M^{\ddagger}$0.52%), 250 (12.32),154 (100), 139 (0.37), 136 (0.81).
66	m/z	277 ($M^{\ddagger}$,1.2%), 250 (15.64), 154 (100), 139 (0.43), 136 (1.00).
67	m/z	310 ($M^{\ddagger}$0.32%), 283 (22.11), 192 (4.31), 151 (100).
68	m/z	324 ($M^{\ddagger}$0.23%), 297 (17.26), 206 (0.91), 177 (0.91), 165 (100), 137 (77.7), 107 (2.40).

Table 8 (continued)

Mass spectral fragmentation of benzylaminoacetonitriles. (electron impact)

Compound		Relative abundancies
69	m/z	324 (M^+ 0.18%) 297 (15.26), 206 (1.00), 177 (0.81), 165 (100), 137 (78), 107 (1.50).
70	m/z	324 (M^+ 0.31%) 297 (12.41), 206 (4.78, 151 (100), 146 (0.90), 131 (0.78), 121 (0.61).
71	m/z	338 (M^+ 0.24%) 311 (22.49%), 220 (3.23), 165 (100), 137 (80.10).
72	m/z	338 (M^+ 4.34%) 311 (10.60), 220 (6.8), 165 (100), 137 (21.38).
73	m/z	294 (M^+ 0.85%) 267 (9.55), 176 (2.86), 135 (100), 132 (1.39), 107 (26.56), 91 (8.33).
74	m/z	244 (M^+ 2.31%), 217 (10.08), 121 (100), 91 (8.55).
75	m/z	258 (M^+ 0.77%), 231 (10.27), 135 (100), 107 (65.71), 91 (1.02).
76	m/z	272 (M^+ 0.42%), 245 (14.63), 148 (100), 121 (20.44), 91 (6.20).
77	m/z	247 (M^+ 0.99%), 217 (14.65), 121 (100), 91 (12.3).
78	m/z	258 (M^+ 0.93%), 231 (21.50), 135 (100), 107 (27.32), 91 (26.71).

4.2 General method for the cyclisation of Benzylaminoacetonitriles

The benzylaminoacetonitrile (3 g) was added carefully to concentrated sulphuric acid (98%, 30 ml) at 0° with continuous stirring. When dissolution was complete, the temperature was raised to room temperature or 50° and stirring continued for a further four hours. In the case of cyclisation at -10°, this temperature was maintained throughout the procedure.

The solution was then poured onto crushed ice and stirred for 45 minutes. The diluted mixture was basified with 5M sodium hydroxide, ice being added from time to time to prevent excessive rise in temperature.

The reaction mixture was extracted with chloroform (5 x 100 ml) washed with water, dried with magnesium sulphate and the solvent removed under reduced pressure to give product(s).

The extracted aqueous solution was reacidified with concentrated hydrochloric acid, basified with potassium hydrogen carbonate, extracted with chloroform (8 x 100 ml), dried with magnesium sulphate and removal of solvent under reduced pressure gave phenolic product(s).

In the case of cyclisation of aminonitriles (61-64) the diluted mixture was basified with concentrated ammonia solution and continuously extracted with chloroform for 24 hours. The chloroform extract was dried ($MgSO_4$), filtered and the removal of solvent under reduced pressure gave the phenolic product(s). However, aminonitriles (77 and 78) failed to cyclise at any of the chosen conditions.

Purification of the cyclised products

Alkoxy products

The cyclised alkoxy products obtained from cyclisation of aminonitriles (58-60, 65,66 and 71-76) were recrystallised from appropriate solvents (tables 9,14 and 23). Cyclisation of aminonitriles (67-69) gave a mixture of products which were separated by column chromatography using silica Woelum (100-200) as stationary phase and ethylacetate as eluent.

A mixture of dialkoxyisoquinolinones was obtained from cyclisation of aminonitrile (70) which was separated by fractional recrystallisation (table 9) using petroleum-ether (60-80°)/ethylacetate (1:1).

Phenolic products

The phenolic products obtained from cyclisation of aminonitriles (58,65,67,71-75) were purified by recrystallisation from appropriate solvents (tables 9,14 and 23).

A mixture of phenolic products was obtained from cyclisation of aminonitrile (59) which was separated by preparative t.l.c. using petroleum-ether (60-80°)/ethylacetate (1:1) as a solvent on a silica gel 60PF stationary phase.

Removal of the two adsorption zones (Rf 0.75 and 0.43) by elution with chloroform gave appropriate phenolic isoquinolinone (table 9)

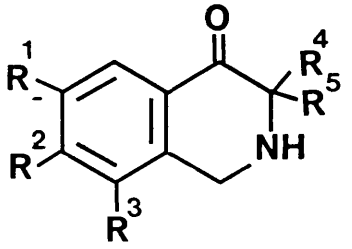
Cyclisation of aminonitriles (61-64 and 67-69) gave

a mixture of products which was separated by column chromatography using silica Woelum (100-200) as a stationary phase and ethylacetate as elutent.

The aminonitriles (59 and 72) upon treatment with concentrated sulphuric acid at room temperature resulted in a mixture of phenolic products, which were separeted by fraction recrystallisation using a mixture of petroleum-ether (60-80^{o})/ ethylacetate.

Table 9

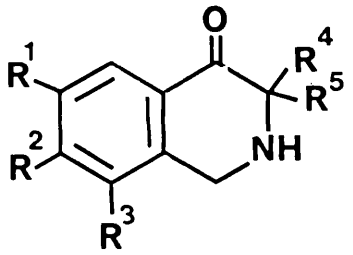
2,3-dihydroisoquinolin-4(1H)-ones.



Compound	R^1	R^2	R^3	R^4 R^5	From nitrile	% yield at -10°C	R.T.	50°C
79	CH_3O	CH_3O	H	$-CH_2(CH_2)_3CH_2-$	58	75	60	15
80	CH_3O	HO	H	$-CH_2(CH_2)_3CH_2-$	58	10	21	65
81	CH_3O	CH_3CH_2O	H	$-CH_2(CH_2)_3CH_2-$	59	72	52	2.6
80	CH_3O	HO	H	$-CH_2(CH_2)_3CH_2-$	59	15	22	65
82	H	HO	CH_3O	$-CH_2(CH_2)_3CH_2-$	59	3	3.9	2.2
83	CH_3CH_2O	CH_3O	H	$-CH_2(CH_2)_3CH_2-$	60	58	20	8
84	HO	CH_3O	H	$-CH_2(CH_2)_3CH_2-$	60	0	25	48
85	CH_3CH_2O	HO	H	$-CH_2(CH_2)_3CH_2-$	60	32	35	0

Table 9 (continued)

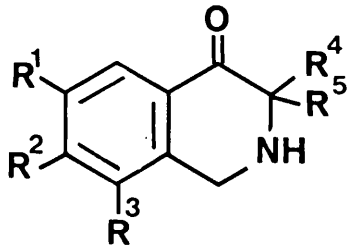
2,3-dihydroisoquinolin-4(1H)-ones



Compound	R^1	R^2	R^3	R^4 R^5	From nitrile	% yield at -10°C	R.T.	50°C
80	CH_3O	HO	H	$-CH_2(CH_2)_3CH_2-$	61	86	80	70
82	H	HO	CH_3O	$-CH_2(CH_2)_3CH_2-$	61	4.0	3.9	3.0
86	HO	HO	H	$-CH_2(CH_2)_3CH_2-$	61	3	4	7
84	HO	CH_3O	H	$-CH_2(CH_2)_3CH_2-$	62	82	75	68
87	H	CH_3O	OH	$-CH_2(CH_2)_3CH_2-$	62	2.8	2.2	2.0
86	HO	HO	H	$-CH_2(CH_2)_3CH_2-$	62	4	7	12
85	CH_3CH_2O	HO	H	$-CH_2(CH_2)_3CH_2-$	63	70	55	5
86	HO	HO	H	$-CH_2(CH_2)_3CH_2-$	63	5	10	18

Table 9 (continued)

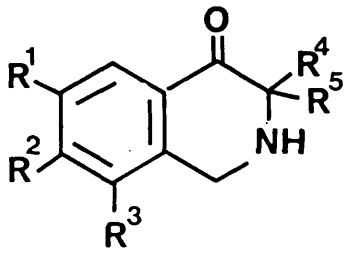
2,3-dihydroisoquinolin-4(1H)-ones



Compound	R^1	R^2	R^3	R^4	R^5	From nitrile	% yield at -10°C	R.T.	50°C
88	HO	CH_3CH_2O	H	$-CH_2(CH_2)_3CH_2-$		64	60	34	3.2
86	HO	HO	H	$-CH_2(CH_2)_3CH_2-$		64	8	14	29
89	CH_3O	CD_3O	H	$-CH_2(CH_2)_3CH_2-$		65	70	60	18
90	CH_3O	HO	H	$-CH_2(CH_2)_3CH_2-$		65	7	25	72
99	CD_3O	CH_3O	H	$-CH_2(CH_2)_3CH_2-$		66	69	62	10
91	CD_3O	HO	H	$-CH_2(CH_2)_3CH_2-$		66	6	29	71
92*	CH_3O	CH_3O	H	CH_3	$-CH_2C_6H_5$	67	69	60	12
93*	CH_3O	HO	H	CH_3	$-CH_2C_6H_5$	67	9	12	57

Table 9 (continued)

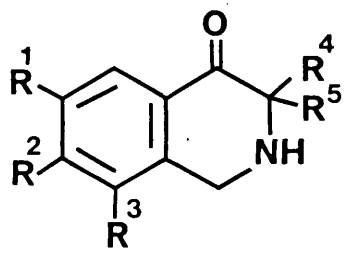
2,3-dihydroisoquinolin-4(1H)-ones



Compound	R^1	R^2	R^3	R^4	R^5	From nitrile	% yield at -10°C	R.T.	50°C
94*	CH_3O	CH_3CH_2O	H	CH_3	$-CH_2C_6H_5$	68	60	50	2.0
93*	CH_3O	HO	H	CH_3	$-CH_2C_6H_5$	68	9	20	62
95*	CH_3CH_2O	CH_3O	H	CH_3	$-CH_2C_6H_5$	69	55	41	3.0
96*	HO	CH_3O	H	CH_3	$-CH_2C_6H_5$	69	0	17	60
97*	CH_3CH_2O	HO	H	CH_3	$-CH_2C_6H_5$	69	20	12	0
98*	CH_3O	CH_3O	H	CH_3	$-CH_2CH_2C_6H_5$	70	54	49	8
99	H	CH_3O	CH_3O	CH_3	$-CH_2CH_2C_6H_5$	70	3.9	2.5	1.2
100	H	HO	CH_3O	CH_3	$-CH_2CH_2C_6H_5$	70	1.3	2.1	3.2

Table 9 (continued)

2,3-dihydroisoquinolin-4(1H)-ones



Compound	R^1	R^2	R^3	R^4	R^5	From nitrile	% yield at -10°C	R.T.	50°C
101	CH_3O	HO	H	CH_3	$-CH_2CH_2C_6H_5$	70	7	14	40
102	CH_3O	CH_3CH_2O	H	CH_3	$-CH_2CH_2C_6H_5$	71	48	40	6
101	CH_3O	HO	H	CH_3	$-CH_2CH_2C_6H_5$	71	14	19	47
103	CH_3CH_2O	CH_3O	H	CH_3	$-CH_2CH_2C_6H_5$	72	51	30	8
104	HO	CH_3O	H	CH_3	$-CH_2CH_2C_6H_5$	72	0	17	32
105	CH_3CH_2O	OH	H	CH_3	$-CH_2CH_2C_6H_5$	72	20	10	0

* see table (13) for data relating to 3-benzoyltetrahydroisoquinolines also obtained in this case.

Table 10

2,3-dihydroisoquinolin-4(1H)-ones

Compound	Formula	m.p.	Recrystallisation solvent pet-ether (60-80°)/ethylacetate	Found %			Required %		
				C	H	N	C	H	N
79	$C_{16}H_{19}NO_3$	147-148 (lit[51] 147)	3:1	Previously characterised[51]					
80	$C_{15}H_{19}NO_3$	161-162 (lit[88] 162)	1:2	Previously characterised[88]					
81	$C_{17}H_{23}NO_3$	114-115 (lit[88] 115)	1:1	Previously characterised[88]					
82	$C_{15}H_{19}NO_3$	202-203	1:1	68.84	7.36	5.76	68.96	7.28	5.36
83	$C_{17}H_{23}NO_3$	164-165 (lit[88] 164	1:0	Previously characterised[88]					
84	$C_{15}H_{19}NO_3$	208-209 (lit[88] 209)	1:1	Previously characterised[88]					
85	$C_{16}H_{21}NO_3$	152-153	3:1	70.23	7.87	5.38	69.79	7.69	5.09

Table 10 (continued)

2,3-dihydroisoquinolin-4(1H)-ones

Compound	Formula	m.p.	Recrystallisation solvent pet-ether (60-80°)/ethylacetate	Found %			Required %		
				C	H	N	C	H	N
86	$C_{14}H_{17}NO_3$	230-231	0:1	68.01	7.08	5.45	67.99	6.73	5.66
87	$C_{15}H_{19}NO_3$	206-207	1:1	68.92	7.31	5.33	68.96	7.28	5.36
88	$C_{16}H_{21}NO_3$	162-163	1:1	69.98	7.71	5.60	69.79	7.69	5.09
92	$C_{19}H_{21}NO_3$	109-110	2:1	73.24	6.92	4.43	73.29	6.79	4.49
93	$C_{18}H_{19}NO_3$	148-149	1:2	72.92	6.37	4.72	72.71	6.44	4.71
94	$C_{20}H_{23}NO_3$	81-82	2:1	73.88	7.13	4.33	73.82	7.12	4.30
95	$C_{20}H_{23}NO_3$	91-92	2:1	74.08	7.14	4.28	73.82	7.12	4.30
96	$C_{18}H_{19}NO_3$	175-176	1:2	72.55	6.58	4.60	72.71	6.44	4.71
97	$C_{19}H_{21}NO_3$	163-164	1:3	73.70	7.29	4.15	73.29	6.80	4.40
98	$C_{20}H_{23}NO_3$	78-79	2:1	73.99	7.13	4.26	73.82	6.12	4.30
99	$C_{20}H_{23}NO_3$	84-85	1:0	73.94	7.14	4.27	73.82	6.12	4.30

Table 10 (continued)

2,3-dihydroisoquinolin-4(1H)-ones

Compound	Formula	m.p.	Recrystallisation solvent pet-ether (60-80°)/ethylacetate	Found %			Required %		
				C	H	N	C	H	N
100	$C_{19}H_{21}NO_3$	163-164	1:1	73.32	6.88	4.51	73.29	6.80	4.49
101	$C_{19}H_{21}NO_3$	173-174	1:4	73.48	6.47	4.14	73.29	6.80	4.49
102	$C_{21}H_{25}NO_3$	75-76	2:1	74.45	7.39	4.22	74.31	7.42	4.13
103	$C_{21}H_{25}NO_3$	82-83	2:1	74.04	7.79	4.12	74.31	7.42	4.13
104	$C_{19}H_{21}NO_3$	167-168	1:3	73.37	6.93	4.38	73.29	6.80	4.49
105	$C_{20}H_{23}NO_3$	122-123	1:2	74.15	7.28	4.48	73.82	7.12	4.30

Table 11

Spectroscopic data for 2,3-dihydroisoquinolin-4(1H)-ones

Compound	ν_{max} /cm^{-1} NH	CO	δ_H (100 MHz; standard TMS).
79	3380	1660	($CDCl_3$) 7.28 (1H,s,C5-H), 6.56 (1H,s,C8-H), 4.03 (2H,s,Ar-$\underline{CH_2}$), 3.92 (6H,s,2 x OCH_3), 2.01 (1H,s,NH)$^{\Phi}$, 1.8-1.2 (10H,m,C_5H_{10}).
80	3380 (+OH)	1675	(DMSO) 7.35 (7.08**,1H,s,C5-H), 6.60 (6.00**,1H,s,C8-H), 3.84 (2H,s,Ar-CH_2), 3.80 (3H,s,OCH_3), 3.0-1.0 (12H*,m,C_5H_{10}+NH+OH).
81	3400	1660	($CDCl_3$) 7.48 (1H,s,C5-H), 6.55 (1H,s,C8-H), 4.2-4.05 (2H,q,$O\underline{CH_2}CH_3$, J=7Hz), 4.0 (2H,s,Ar-$\underline{CH_2}$), 3.84 (3H,s,OCH_3), 1.97 (1H,s,NH)$^{\Phi}$, 1.80-1.50 (10H,m, C_5H_{10}), 1.45 (3H,t,$OCH_2\underline{CH_3}$, J=7Hz.
82	3375	1665	(DMSO) 7.60 (7.35**, 1H,d,C5-H, J=8Hz), 6.70 (6.15**,1H,d,C6-H, J=8Hz), 3.90 (3.80**,2H,s,Ar-$\underline{CH_2}$-), 3.70 (3.60**,3H,s,OCH_3), 1.80-1.20 (11H*,m, C_5H_{10}+NH).
83	3350	1645	($CDCl_3$) 7.50 (1H,s,C5-H), 6.54 (1H,s,C8-H), 4.21-4.02 (2H,q,$O\underline{CH_2}CH_3$, J=7Hz), 4.0 (2H,s,Ar-$\underline{CH_2}$), 3.89 (3H,s,OCH_3), 1.93 (1H,s,NH)$^{\Phi}$, 1.84-1.50 (10H,m,C_5H_{10}), 1.49 (3H,t,$OCH_2\underline{CH_3}$,J=7Hz).
84	3370 (+OH)	1650	(DMSO) 9.2 (1H,s,OH)$^{\Phi}$, 7.24 (6.78**1H,s,C5-H), 6.76 (6.45**,1H,s,C8-H), 3.87 (2H,s,Ar-$\underline{CH_2}$), 3.80 (3H,s,OCH_3), 1.56 (11H*,m,NH+C_5H_{10}).

Table 11 (continued)

Spectroscopic data for 2,3-dihydroisoquinolin-4(1H)-ones

Compound	ν_{max} /cm^{-1} NH	CO	δ_H (100 MHz; standard TMS).
85	3360 (+OH)	1650	(DMSO) 7.25 (7.08**,1H,s,C5-H), 6.30 (6.0**,1H,s,C8-H), 4.18-4.00 (2H, q,O<u>CH$_2$</u>CH$_3$, J=7Hz), 3.80 (2H,s,Ar-<u>CH$_2$</u>-), 1.6 (12H*,broad m, C_5H_{10}+NH+OH), 1.29-1.25 (3H,t,OCH$_2$CH$_3$, J=7Hz).
86	3375	1680	(DMSO) 7.26 (6.62**,1H,s,C5-H), 6.54 (5.86**,1H,s,C8-H), 3.82 (2H,s,Ar-<u>CH$_2$</u>-), 1.82-1.22 (13H*,broad s,+C_5H_{10}+NH+2 x OH).
87	3390	1670	(DMSO) 7.4 (1H,d,C5-H, J=8Hz), 7.0 (1H,d,C6-H, J=8Hz), 3.86 (3H,s,OCH$_3$), 3.64 (2H,s,Ar-<u>CH$_2$</u>-), 2.0-1.0 (12H*,m,C_5H_{10}+NH+OH).
88	3380 (+OH)	1685	(DMSO) 9.1 (1H,broad s,OH)$^{\alpha}$, 7.28 (7.04**,1H,s,C5-H), 6.70 (6.53**,1H,s,C8-H), 4.20-4.00 (2H,q,O<u>CH$_2$</u>CH$_3$, J= 7Hz), (2H,s,Ar-CH$_2$-), 2.8 (1H,broad s,NH), 1.8-1.48 (10H,m,C_5H_{10}), 1.42-1.29 (3H,t,OCH$_2$<u>CH$_3$</u>, J=7Hz).
89	3350	1680	($CDCl_3$) 7.24 (1H,s,C5-H), 6.51 (1H,s,C8-H), 3.98 (2H,s,Ar-<u>CH$_2$</u>-), 3.87 (3H,s,OCH$_3$), 2.2 (1H,broad s,NH)$^{\alpha}$, 1.8-1.4 (10H,m,C_5H_{10}).
90	3345	1675	($CDCl_3$), 7.25 (1H,s,C5-H), 6.55 (1H,s,C8-H), 3.97 (2H,s,Ar-<u>CH$_2$</u>-), 3.88 (3H,s, OCH$_3$), 2.2 (1H,broad s,NH)$^{\alpha}$, 1.85-1.45 (10H,m,C_5H_{10}).

Table 11 (continued)

Spectroscopic data for 2,3-dihydroisoquinolin-4(1H)-ones

Compound	ν_{max} /cm^{-1} NH(OH)	CO	δ_H (100 MHz; standard TMS).
91	3400 (+OH)	1670	(DMSO), 7.25 (7.00**, 1H,s,C5-H), 6.55 (5.95**, 1H,s,C8-H), 3.97 (2H,s,Ar-CH_2-), 1.8-1.1 (12H,m,C_5H_{10}+NH+OH).
92	3280	1670	($CDCl_3$), 7.56 (1H,s,C5-H), 7.4-7.2 (5H,m,-CH_2-Ar), 6.62 (1H,s,C8-H) 4.2 (2H,s,-CH_2-NH-), 3.92 (6H,s,2 x OCH_3), 3.52-3.36 and 2.86-2.73 (2H,ABq, -CH_2-Ar, J=12Hz), 2.4 (1H,s,NH)$^{\Phi}$, 1.34 (3H,s,CH_3).
93	3300 (3450)	1670	(DMSO), 7.20 (7.13**,1H,s,C5-H), 7.24 (5H,s,-CH_2-Ar), 6.64 (5.95**,1H,s,C8-H), 3.96 (3.76**,2H,s,-CH_2-NH-), 3.80 (3.66**,3H,s,OCH_3), 3.16-3.12), and 2.80-2.65 (2.69**-2.56), 2H,ABq,-CH_2-Ar, J=12Hz), 2.22 (2H,s,NH+OH)$^{\Phi}$, 1.07 (3H,s,CH_3).
94	3350	1675	($CDCl_3$) 7.32 (1H,s,C5-H), 7.23 (5H,s,-CH_2-Ar), 6.52 (1H,s,C8-H), 4.20-4.00 (2H,q,OCH_2CH_3, J=7Hz), 4.07 (2H,s,-CH_2-NH-), 3.90 (3H,s,OCH_3), 3.40-3.36 and 3.82-2.69 (2H,ABq,-CH_2-Ar, J=12Hz), 2.09 (1H,s,NH)$^{\Phi}$, 1.54-1.40 (3H,t,OCH_2CH_3, J=7Hz), 1.31 (3H,s,CH_3).

Table 11 (continued)

Spectroscopic data for 2,3-dihydroisoquinolin-4(1H)-ones

Compound	ν_{max} /cm^{-1} NH(OH)	CO	δ_H (100 MHz; standard TMS).
95	3340	1675	($CDCl_3$) 7.54 (1H,s,C5-H), 7.25 (5H,s,CH_2-Ar), 6.55 (1H,s,C8-H), 4.28-4.0 (2H, q,OCH_2CH_2, J=7Hz), 4.11 (2H,s,-CH_2-NH-), 3.90 (3H,s,OCH_3) 3.51-3.36 and 2.83-2.70 (2H,ABq,-CH_2-Ar, J=L2Hz), 2.09 (1H,s,NH)$^{\Phi}$, 1.54-1.40 (3H,t, OCH_2CH_3, J=7Hz), 1.32 (3H,s,CH_3).
96	3305 (3430)	1670	(DMSO), 9.30 (1H,broad s,OH)$^{\Phi}$, 7.34 (6.96**,1H,s,C5-H), 7.21 (5H,s,CH_2-Ar), 6.78 (6.48**,1H,s,C8-H), 4.0 (2H,s,-CH_2-NH-), 3.84 (3H,s,OCH_3), 3.12-3.0 and 2.82-2.68 (2H,ABq,-CH_2Ar, J=12Hz), 1.4-1.0 (4H,s,CH_3+NH)††.
97	3295 (3450)	1675	(DMSO), 7.36 (7.16**,1H,s,C5-H), 7.3-7.1 (5H,m,CH_2-Ar),(6.65**,1H,s, C8-H), 4.12-3.84 (2H,q,OCH_2CH_3, J=7Hz), 3.90 (2H,s,-CH_2-NH-), 3.12-3.00 and 2.78-2.64 (2H,ABq,-CH_2-Ar, J=12Hz), 1.4-1.25 (3H,t,OCH_2CH_3, J=7Hz), 1.06 (5H,s,CH_3+NH+OH)††.
98	3300	1670	($CDCl_3$) 7.52 (1H,s,C5-H), 7.24 (5H,m,CH_2CH_2-Ar), 6.56 (1H,s,C8-H), 4.07 (2H,s,-CH_2-NH-), 3.88 (6H,s,2 x OCH_3), 2.80-2.62 (2H,t,-CH_2-CH_2Ar, J=8Hz), 2.34 (1H,s,NH)$^{\Phi}$, 2.20-1.80 (2H,m,-CH_2CH_2Ar), 1.37 (3H,s,CH_3).

Table 11 (continued)

Spectroscopic data for 2,3-dihydroisoquinolin-4(1H)-ones

Compound	ν_{max} /cm^{-1} NH(OH)	CO	δ_H (100 MHz; standard TMS).
99	3295	1660	($CDCl_3$) 7.88-7.78 (1H,d,C5-H, J=8Hz), 7.28-7.09 (5H,m,-CH_2CH_2-Ar), 6.68-6.58 (1H,d,C6-H, J=8Hz), 4.18 (2H,s,-CH_2-NH-), 3.92 (3H,s,OCH_3), 3.84 (3H,s,OCH_3), 2.80-2.60 (2H,t,-CH_2CH_2Ar, J=8Hz), 2.16 (1H,s,NH)$^{\Phi}$, 2.0-1.72 (2H,m,-CH_2CH_2-Ar), 1.37 (3H,s,CH_3(.
100	3250	1680	(DMSO), 9.29 (1H,broad s,OH)$^{\Phi}$, 7.78 (7.53**,1H,d,C5-H, J=8Hz), 7.34-7.14 (5H, m,-CH_2CH_2Ar), 6.51 (5.91**,1H,d,C6-H, J=8Hz), 4.02 (2H,s,-CH_2-NH-), 3.86 (3H,s,OCH_3), 2.80-2.62 (2H,t,-CH_2CH_2Ar, J=8Hz), 2.14 (1H,s,NH)$^{\Phi}$, 2.00-1.68 (2H,m,-CH_2CH_2Ar), 1.36 (3H,s,CH_3).
101	3295	1675	(DMSO) 9.2 (1H,s,OH)$^{\Phi}$, 7.42 (7.26**,1H,s,C5-H), 7.36-7.10 (5H,m,-CH_2CH_2Ar), 6.50 (5.88**,1H,s,C8-H), 2.80-2.50 (2H,t,-CH_2-CH_2-Ar,J=8Hz), 2.12-1.4 (2H,m, -CH_2CH_2-Ar), 1.24 (3H,s,CH_3).
102	3370	1680	($CDCl_3$) 7.48 (1H,s,C5-H), 7.28-7.08 (5H,m,CH_2CH_2-Ar), 6.52 (1H,s,C8-H), 4.2-4.0 (2H,q,OCH_2CH_3, J=7Hz), 4.06 (2H,s,-CH_2-NH-), 3.88 (3H,s,OCH_3), 2.80-2.60 (2H,t,-CH_2CH_2-Ar, J=8Hz), 2.14 (1H,s,NH)$^{\Phi}$, 2.08-1.68 (2H,m,-CH_2 CH_2Ar), 1.58-1.40 (3H,t,OCH_2CH_3, J=7Hz), 1.36 (3H,s,CH_3).

Table 11 (continued)

Spectroscopic data for 2,3-dihydroisoquinolin-4(1H)-ones

Compound	ν_{max} /cm^{-1} NH(OH)	CO	δ_H (100 MHz; standard TMS).
103	3360	1675	($CDCl_3$) 7.52 (1H,s,C5-H), 7.36-7.08 (5H,m,-CH_2CH_2-<u>Ar</u>), 6.55 (1H,s,C8-H), 4.20-4.00 (2H,q,OCH_2CH_3, J=8Hz), 4.04 (2H,s,-<u>CH_2</u>-NH-), 3.86 (3H,s,OCH_3), 2.78-1.60 (2H,t,-CH_2<u>CH_2</u>Ar, J=8Hz), 2.12 (1H,s,NH)$^{\Theta}$, 2.2-1.8 (2H,m,-<u>CH_2</u>CH_2Ar), 1.52-1.40 (3H,t,OCH_2<u>CH_3</u>, J=8Hz), 1.36 (3H,s,CH_3).
104	3290 (3450)	1675	(DMSO) 7.40 (6.72**.1H,s,C5-H), 7.36-7.15 (5H,m,CH_2CH_2<u>Ar</u>), 6.68 (6.54**, 1H,s,C8-H), 3.94 (2H,s,-<u>CH_2</u>-NH-), 3.84 (3H,s,OCH_3), 2.80-2.52 (2H,t, -CH_2<u>CH_2</u>Ar, J=8Hz), 2.12-1.40 (3H*,m,-<u>CH_2</u>CH_2Ar+NH), 1.25 (1H,s,CH_3).
105	3100	1680	(DMSO) 7.40 (7.35**,1H,s,C5-H), 7.32-7.08 (5H,m,-CH_2CH_2-<u>Ar</u>), 6.68 (6.50**, 1H,s,C8-H), 4.20-3.90 (2H,q,O<u>CH_2</u>CH_3, J=7Hz), 3.96 (2H,s,-<u>CH_2</u>-NH), 2.80-2.50 (2H,t,-CH_2<u>CH_2</u>Ar, J=8Hz), 2.08-1.60 (2H,m,-<u>CH_2</u>CH_2Ar), 1.40-1.26 (3H, t,OCH_2<u>CH_3</u>, J=7Hz), 1.24 (3H,s,CH_3).
134	3400	1675	(DMSO) 7.26 (6.76**,1H,s,C5-H), 6.77 (6.50**,1H,s,C8-H), 3.84 (2H,s,Ar-<u>CH_2</u>), 1.62-1.22 (11H,m,NH+C_5H_{10}).

* reduced to 10 after deuteration
** after addition of NaOD in D_2O
|| reduced to 3 after deuteration
Θ disappeared after deuteration

Table 12

Mass spectral fragmentation of 2,3-dihydroisoquinolin-4(1H)-ones. (Electron impact)

Compound		Relative abundancies
79	m/z	275 (M^{+}52.13%), 247 (18.39), 232 (3.12), 203 (13.12), 178 (8.12), 151 (100), 150 (5.38).
80	m/z	261 (M^{+}76%), 233 (17.13), 218 (9.16), 190 (20.73), 176 (4.80), 165 (14.65), 164 (39.13), 137 (100), 135 (25.12).
81	m/z	289 (M^{+}41.16%), 287 (3.25), 261 (8.36), 233 (2.18), 218 (11.02), 192 (35.73), 166 (10.57), 165 (100), 164 (13.89), 137 (10.07).
82	m/z	261 (M^{+}51.71%), 233 (5.32), 218 (7.35), 208 (11.97), 202 (59.83), 192 (4.41), 190 (22.52), 176 (23.69), 165 (8.92), 164 (9.40), 152 (34.44), 149 (64.50), 137 (26.12).
83	m/z	289 (M^{+}48.94%), 261 (10.52), 233 (1.86), 218 (19.94), 192 (40.40), 166 (9.89), 165 (100), 164 (20.46), 137 (57.87).
84	m/z	261 (M^{+}74.67%), 259 (1.76), 233 (17.12), 218 (7.72), 192 (1.09), 190 (20.20), 176 (3.47), 164 (36.84), 137 (100), 136 (20.87).
85	m/z	275 (M^{+}64.32%), 247 (18.36), 246 (8.36), 218 (13.39), 178 (36.77), 151 (100), 137 (4.76), 123 (55.99), 122 (11.49).

Table 12 (continued)

Mass spectral fragmentation of 2,3-dihydroisoquinolin-4(1H)-ones. (Electron impact)

Compound		Relative abundancies
86	m/z	247 (M^+89.78%), 219 (39.98), 176 (21.08), 150 (15.32), 123 (100), 122 (17.18).
87	m/z	261 (M^+39.60%), 233 (27.36), 218 (7.39), 216 (19.52), 190 (16.93), 165 (4.32), 164 (14.2), 153 (24.55), 152 (19.77), 148 (20.09), 137 (100), 136 (27.27), 122 (15.60).
88	m/z	275 (M^+66.49%), 247 (18.54), 246 (12.14), 218 (9.86), 204 (27.68), 178 (45.16), 151 (100), 123 (58.76), 122 (19.91), 98 (34.51), 97 (83.52).
89	m/z	278 (M^+28.73%), 250 (7.19), 235 (4.05), 207 (13.28), 181 (26.), 154 (100).
90	m/z	278 (M^+31.11%), 250 (10.56), 235 (2.16), 207 (16.18), 181 (32), 154 (100).
91	m/z	264 (M^+37.38%), 236 (15.15), 221 (2.04), 181 (12.88), 167 (29.33), 154 (35.45), 140 (100), 139 (19.42).
92	m/z	311 (M^+0.21%), 309 (1.59), 220 (100), 192 (5.39), 178 (5.14), 151 (24.27), 150 (7.67).
93	m/z	297 (M^+0.74%), 295 (2.11), 268 (1.02), 207 (11.91), 200 (100), 179 (8.93), 164 (8.41), 137 (28.58), 136 (8.51).

Table 12 (continued)

Mass spectral fragmentation of 2,3-dihydroisoquinolin-4(1H)-ones. (Electron impact)

Compound		Relative abundancies
94	m/z	325 (M^+ 0.30%), 323 (7.49), 234 (100), 206 (11.09), 178 (6.15), 176 (5.71), 165 (24.76), 164 (6.97), 162 (1.89), 161 (3.05), 149 (6.52), 137 (8.63), 136 (8.04).
95	m/z	325 (M^+ 1.11%), 234 (100), 206 (8.6), 192 (4.06), 178 (3.05), 165 (9.66), 164 (6.74), 137 (17.77), 136 (5.01).
96	m/z	297 (M^+ 3.14%), 268 (o.98), 207 (14.75), 206 (100), 178 (11.49), 164 (6.50), 148 (4.71), 137 (32.51), 136 (10.38), 108 (8.11).
97	m/z	311 (M^+ 0.92%), 220 (100), 192 (9.40), 178 (5.38), 164 (4.12), 151 (12.97), 150 (5.67), 123 (18.49), 122 (6.59).
98	m/z	325 (M^+ 2.75%), 310 (4.07), 297 (4.47), 220 (100), 192 (15.94), 178 (27.33), 151 (90.80), 150 (23.19), 136 (1.61).
99	m/z	325 (M^+ 2.19%), 297 (2.78), 220 (100), 206 (14.80), 192 (20.46), 178 (30.62), 165 (5.97), 151 (95.51), 150 (31), 136 (2.50).

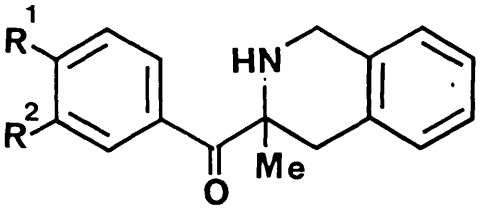
Table 12 (continued)

Mass spectral fragmentation of 2,3-dihydroisoquinolin-4(1H)-ones. (Electron impact)

Compound		Relative abundancies
100	m/z	311 (M^+3.26%), 283 (6.31), 206 (100), 192 (18.68), 178 (11.88), 165 (3.66), 164 (25.32), 151 (3.33), 137 (66.83), 136 (12.79).
101	m/z	311 (M^+2,67%), 283 (4.76), 206 (100), 192 (21.26), 178 (13.26), 165 (3.80), 164 (21.17), 151 (4.22), 137 (68.44), 136 (17.20).
102	m/z	339 (M^+2.53%), 234 (100), 220 (12.63), 206 (16.20), 192 (35.10), 178 (5.26), 165 (79.18), 164 (20.10), 137 (15.31), 136 (14.11).
103	m/z	339 (M^+2.86%), 234 (100), 220 (11.40), 206 (17.81), 192 (34.65), 178 (8.05), 165 (76.77), 164 (21.10), 137 (17.38), 136 (14.87).
104	m/z	311 (M^+2.65%), 283 (3.53), 206 (100), 192 (20.53), 178 (14.75), 165 (4.36), 164 (20.32), 151 (5.86), 137 (82.25), 136 (18.96).
105	m/z	325 (M^+1.34%), 297 (1.76), 220 (100), 206 (18.30), 192 (13.39), 178 (16.66), 176 (11.38), 151 (30.69), 150 (13.52), 138 (8.12), 137 (12.47), 136 (4.60).
134	m/z	264 (M^+31.49%), 236 (20.13), 221 (5.34), 181 (10.77), 167 (32.01), 154 (40.38).

Table 13

3-benzoyltetrahydroisoquinolines



Compound	R^1	R^2	From nitrile	% yield at -10°C	R.T.	50°C
106	CH_3O	CH_3O	67	12	10	2
107	HO	CH_3O	67	2	3	2
108	CH_3CH_2O	CH_3O	68	14	10	0.4
107	HO	CH_3O	68	2	4	16
109	CH_3O	CH_3CH_2O	69	12	8	0.5
110	CH_3O	HO	69	0	3.5	12
111	HO	CH_3CH_2O	69	4	3	0
112	CH_3CH_2O	H	73	79	65	4
113	HO	H	73	10	20	78

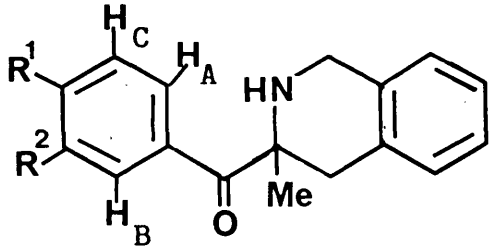
Table 14

3-benzoyltetrahydroisoquinolines

Compound	Formula	m.p. (°C)	Recrystallisation solvent pet-ether (60-80°)/ethylacetate	Found %			Required %		
				C	H	N	C	H	N
106	$C_{19}H_{21}NO_3$	138-139 (lit[66] 130)	1:0	Previously characterised[66]					
107	$C_{18}H_{19}NO_3$	156-157	1:1	72.59	6.41	4.52	72.71	6.44	4.71
108	$C_{20}H_{23}NO_3$	80-81	1:0	73.85	6.99	4.30	73.82	7.12	4.30
109	$C_{20}H_{23}NO_3$	89-90	1:0	73.73	7.01	4.29	73.82	7.12	4.30
110	$C_{19}H_{19}NO_3$	147-148	1:1	72.84	6.33	4.74	72.71	6.44	4.71
111	$C_{19}H_{21}NO_3$	165-166	1:2	73.55	7.05	4.32	73.29	6.80	4.49
112	$C_{19}H_{21}NO_2$	73-74	1:0	77.16	7.30	4.56	77.26	7.17	4.74
113	$C_{17}H_{17}NO_2$	205-206	0:1	76.24	6.46	5.23	76.38	6.41	5.24

Table 15

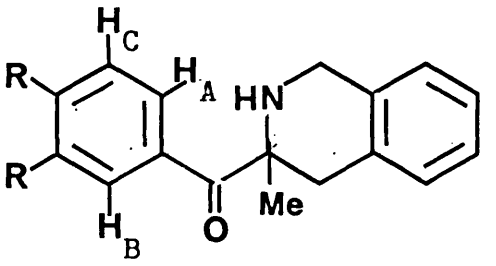
Spectroscopic data for 3-benzoyltetrahydroisoquinolines



Compound	ν_{max} /cm^{-1} NH(OH)	CO	δ_H (100 MHz; standard TMS).
106	3260	1660	($CDCl_3$) 8.18 and 8.08 (1H,dd,H_A,J=2Hz), 7.70 (1H,d,H_B,J=2Hz), 7.08-6.80 (4H,m,C_6H_4), 6.76-6.66 (1H,d,H_C,J=8Hz), 3.80 (8H,2 x s,2 x OCH_3 +-NH-$\underline{CH_2}$-), 3.56-3.40 and 2.66-2.46 (2H,ABq,C4-$\underline{H_2}$,J=16Hz), 2.0 (1H ,s, NH)$^{\Phi}$, 1.52 (3H,s,CH_3).
107	3305 (3450)	1680	(DMSO) 8.24 (8.14**) and 8.14 (8.04**) (1H,dd,H_A,J=2Hz), 7.93 (7.56**) (1H, d,H_B,J=2Hz), 7.12-6.90 (4H,m,C_6H_4), 6.88-6.76 (6.18-6.09**) (1H,d,H_C,J=8Hz), 3.80 (5H,s,OCH_3+-HN-$\underline{CH_2}$-), 3.48-3.32 and 2.62-2.45 (2H,ABq,C4-$\underline{H_2}$,J=16Hz), 1.48 (3H,s,CH_3).
108	3290	1675	($CDCl_3$), 8.24 and 8.16 (1H,dd,H_A,J=2Hz), 7.60 (1H,d,H_B,J=2Hz), 7.12-6.96 (4H, m,C_6H_4), 6.84-6.72 (1H,d,H_C,J=8Hz), 4.20-4.00 (2H,q,$O\underline{CH_2}CH_3$,J=7Hz), 3.96 (2H,s,-HN-$\underline{CH_2}$-), 3.80 (3H,s,OCH_3), 3.60-3.44 and 2.70-2.52 (2H,ABq, C4-$\underline{H_2}$,J=16Hz), 1.53 (3H,s,CH_3), 1.48-1.40 (3H,t,$OCH_2\underline{CH_3}$,J=7Hz).

Table 15 (continued)

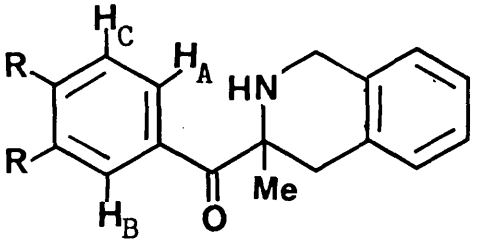
Spectroscopic data for 3-benzoyltetrahydroisoquinolines



Compound	ν_{max} /cm^{-1} NH(OH)	CO	δ_H (100 MHz; standard TMS).
109	3300	1670	($CDCl_3$) 8.25 and 8.18 (1H,dd,H_A, J=2Hz), 7.50 (1H,d,H_B, J=2Hz), 7.12-6.96 (4H,m,C_6H_4), 6.84-6.72 (1H,d,H_C, J=8Hz), 4.22-4.00 (2H,q,$O\underline{CH_2}CH_3$, J=7Hz), 3.96 (2H,s,-NH-$\underline{CH_2}$), 3.82 (3H,s,OCH_3), 3.60-3.45 and 2.70-2.52 (2H, ABq,C4-$\underline{H_2}$, J=16Hz), 1.55 (3H,s,CH_3), 1.50-1.42 (3H,t,$OCH_2\underline{CH_3}$, J=7Hz).
110	3320	1700	(DMSO), 8.25 (8.23**) and 8.15 (8.12**), 1H,dd,H_A, J=2Hz), 7.92 (7.34**) (1H, d,H_B, J=2Hz), 7.14-6.88 (4H,m,C_6H_4), 6.88-6.76 (6.72-6.62**), (1H,d,H_C, J=8Hz), 3.84 (5H,s,OCH_3+-NH-$\underline{CH_2}$-), 3.48-3.32 and 2.63-2.46 (2H,ABq,C4-$\underline{H_2}$, J=16Hz), 1.50 (3H,s,CH_3).
111	3290 (3500)	1675	(DMSO), 7.88 (7.80**), and 7.80 (7.70**), (1H,dd,H_A, J=2Hz), 7.40-7.00 (4H, m,C_6H_4), 6.88-6.80 (6.38-6.30**, (1H,d,H_C, J=8Hz), 4.20-4.00 (2H,q,$O\underline{CH_2}CH_3$, J=7Hz), 4.00 (2H,s,-NH-$\underline{CH_2}$-), 3.48-3.32 and 3.63-2.46 (2H,ABq,C4-$\underline{H_2}$, J=16Hz), 1.40-1.26 (3H,t,$OCH_2\underline{CH_3}$, J=7Hz), 1.28 (3H,s,CH_3)

Table 15 (continued)

Spectroscopic data for 3-benzyoltetrahydroisoquinolines



Compound	ν_{max} /cm^{-1} NH(OH)	CO	δ_H (100 MHz; standard TMS).
112	3340	1680	($CDCl_3$)), 8.4-8.26 (2H,d,AA^1xx^1, J=8Hz), 7.12-6.90 (4H,m,C_6H_4), 6.82-6.72 (2H,d,AA^1xx^1, J=8Hz), 4.0-3.84 (2H,q,$O\underline{CH_2}CH_3$, J=8Hz), 3.82 (2H, s,-CH_2-NH-), 3.52-3.36 and 2.60-2.45 (2H,ABq,C4-$\underline{H_2}$, J=16Hz), 1.8 (1H,s, NH), 1.48 (3H,s,CH_3), 1.38-1.24 (3H,t,$OCH_2\underline{CH_3}$, J=8Hz).
113	3340 (3500)	1695	(DMSO) 8.48-8.28 (2H,d,AA^1xx^1, J=8Hz), 7.1-6.98 (4H,m,C_6H_4), 6.88-6.80 (2H,d,AA^1xx^1, J=8Hz), 4.0-3.56 (2H,q, J=16Hz), 3.56-3.32 and 2.64-2.48 (2H,ABq,C4-$\underline{H_2}$, J=16Hz), 1.46 (3H,s,CH_3).

** After addition of 30% NaOD in D_2O

đ Disappeared after deuteration.

Table 16

Mass spectral fragmentation of 3-benzoyltetrahydroisoquinolines

Compound		Relative abundancies
106	m/z	311 (M^+1.16%), 165 (5.31), 146 (100), 144 (19.95), 137 (1.30), 131 (3.18), 130 (7.07), 104 (4.32).
107	m/z	297 (M^+2.18%), 151 (6.89), 146 (100), 123 (1.99), 131 (4.51), 104 (5.99).
108	m/z	325 (M^+1.08%), 179 (2.75), 151 (6.25), 146 (79.31), 131 (1.48), 104 (6.89).
109	m/z	325 (M^+3.12%), 179 (4.32), 151 (5.40), 146 (100), 131 (2.32), 104 (9.32).
110	m/z	297 (M^+3.11%), 151 (6.31), 146 (100), 131 (10.31), 123 (4.31), 104 (9.32).
111	m/z	311 (M^+0.96%), 165 (7.34), 146 (100), 137 (2.1), 131 (4.01), 109 (3.1), 104 (8.87).
112	m/z	295 (M^+0.85%0, 149 (12.52), 146 (100), 131 (4.01), 109 (3.1), 104 (10.32).
113	m/z	267 (M^+0.16%0, 146 (100), 131 (5.64), 121 (7.26), 1o4 (3.28), 93 (2.70).

Table 17

The ultra-violet spectroscopic data of the phenolic isoquinolinones and phenolic tetrahydroisoquinolines

	Neutral			Alkaline		
Compound	λ_{max}	$E^{1\%}_{1cm}$	logϵ	λ_{max}	$E^{1\%}_{1cm}$	logϵ
80	314	300	3.89	351	900	4.37
82	314	290	3.87	350	750	4.30
84	320	210	3.75	367	156	3.61
85	313	310	3.93	348	836	4.36
87	321	150	3.59	369	116	3.48
88	319	210	3.76	364	190	3.72
91	313	310	3.91	349	700	4.26
93	314	300	3.94	350	895	4.42
96	319	210	3.79	365	168	3.69
97	314	252	3.89	350	900	4.44

Table 17 (continued)

The ultra-violet spectroscopic data of the phenolic isoquinolinones and phenolic tetrahydroisoquinolines

Compound	Neutral			Alkaline		
	λ_{max}	$E^{1\%}_{1cm}$	logϵ	λ_{max}	$E^{1\%}_{1cm}$	logϵ
100	314	290	3.95	350	812	4.39
101	315	284	3.94	350	916	4.45
104	320	178	3.74	364	135	3.62
105	313	280	3.95	351	908	4.45
107	298	210	3.80	345	335	3.99
110	317	140	3.62	366	129	3.58
111	305	250	3.89	350	745	4.36
113	313	250	3.82	348	827	4.34
134	318	207	3.73	363	190	3.69
145	313	250	3.84	351	883	4.40

4.3 4-benzyl-hydroxy-1,2,3,4-tetrahydroisoquinolines

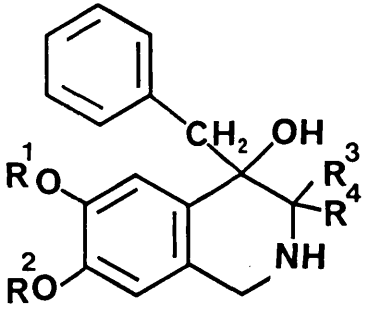
General method

The tetrahydroisoquinolinone (0.5 g), dissolved in dry ether was added dropwise to a cold solution of benzylmagnesium chloride (Grignard reagent 0.1) in dry ether with continuous stirring.

The reaction mixture was stirred for a further two hours, poured onto crushed ice (200 g) and acidified with dilute hydrochloric acid. The aqueous phase was washed twice with ether, basified with ammonia solution and extracted with ether (3 x 100 ml). Dried ($MgSO_4$) filtered and removal of the ether followed by recrystallisation from petroleum-ether (60-80°) gave the required 4-benzyl-4--hydroxy-1,2,3,4-tetrahydroisoquinolines. (Table 18)

Table 18

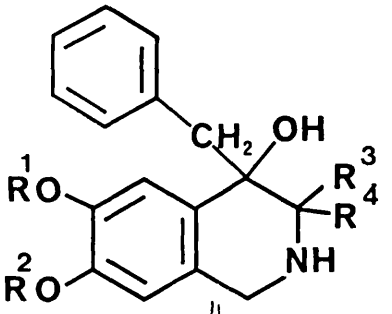
4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines



Compd.	Formula	R^1	R^2	R^3	R^4	Yield (%)	m.p. (°C)	Found % C	Found % H	Found % N	Required % C	Required % H	Required % N
114*	$C_{23}H_{29}NO_3$	CH_3	CH_3	$-CH_2(CH_2)_3CH_2-$		67	171(lit[88]171)	Previously charaterised[88]					
115	$C_{24}H_{31}NO_3$	CH_3	CH_3CH_2	$-CH_2(CH_2)_3CH_2-$		63	148(lit[88]148)	Previously charaterised[88]					
116	$C_{24}H_{31}NO_3$	CH_3CH_2	CH_3	$-CH_2(CH_2)_3CH_2-$		60	183(lit[88]183)	Previously charaterised[88]					
117	$C_{22}H_{27}NO_3$	CH_3	H	$-CH_2(CH_2)_3CH_2-$		59	184-185(lit[88]184)	Previously charaterised[88]					
118	$C_{22}H_{29}NO_3$	H	CH_3	$-CH_2(CH_2)_3CH_2-$		62	150(lit[88]150)	Previously charaterised[88]					
119	$C_{23}H_{29}NO_3$	CH_3CH_2	H	$-CH_2(CH_2)_3CH_2-$		60	172	75.32	8.16	3.75	75.17	7.86	3.81
120	$C_{23}H_{29}NO_3$	H	CH_3CH_2	$-CH_2(CH_2)_3CH_2-$		68	179	75.18	7.99	3.80	75.17	7.86	3.81
121	$C_{26}H_{29}NO_3$	CH_3	CH_3	CH_3	$-CH_2C_6H_5$	72	205-206	77.39	7.32	3.32	77.39	7.24	3.47
122	$C_{27}H_{31}NO_3$	CH_3	CH_3CH_2	CH_3	$-CH_2C_6H_5$	79	170-171	77.66	7.34	3.43	77.67	7.48	3.35

Table 18 (continued)

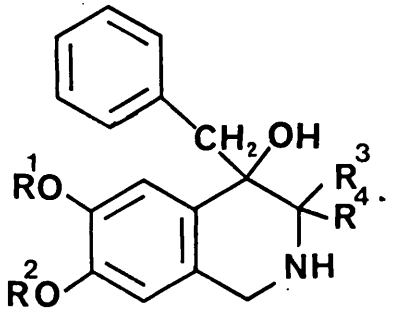
4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines



Compound	Formula	R^1	R^2	R^3	R^4	Yield (%)	m.p. (°C)	Found % C	Found % H	Found % N	Required % C	Required % H	Required % N
123	$C_{25}H_{29}NO_3$	CH_3	H	CH_3	$-CH_2C_6H_5$	75	178-179	76.95	6.98	3.67	77.09	6.99	3.60
124	$C_{27}H_{31}NO_3$	CH_3CH_2	CH_3	CH_3	$-CH_2C_6H_5$	78	169-170	77.72	7.39	3.38	77.69	7.48	3.35
125	$C_{25}H_{27}NO_3$	H	CH_3	CH_3	$-CH_2C_6H_5$	73	195-196	77.01	7.11	3.66	77.09	6.99	3.60
126	$C_{26}H_{29}NO_3$	CH_3CH_2	H	CH_3	$-CH_2C_6H_5$	66	182-183	77.14	7.12	3.47	77.39	7.24	3.47
127	$C_{27}H_{31}NO_3$	CH_3	CH_3	CH_3	$-CH_2CH_2C_6H_5$	79	152-153	77.71	7.72	3.14	77.67	7.48	3,35
128	$C_{28}H_{33}NO_3$	CH_3	CH_3CH_2	CH_3	$-CH_2CH_2C_6H_5$	80	138-139	77.97	7.72	3.32	77.93	7.71	3.24
129	$C_{26}H_{29}NO_3$	CH_3	H	CH_3	$-CH_2CH_2C_6H_5$	68	194-195	77.42	7.34	3.57	77.39	7.24	3.49
130	$C_{28}H_{33}NO_3$	CH_3CH_2	CH_3	CH_3	$-CH_2CH_2C_6H_5$	83	141.142	78.03	7.83	3.33	77.93	7.71	3.24

Table 18 (continued)

4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines



Compound	Formula	R^1	R^2	R^3	R^4	Yield (%)	m.p. (°C)	C	H	N	C	H	N
131	$C_{26}H_{29}NO_3$	H	CH_3	CH_3	$-CH_2CH_2C_6H_5$	69	172.173	77.53	7.36	3.39	77.39	7.24	3.47
132	$C_{27}H_{31}NO_3$	CH_3CH_2	H	CH_3	$-CH_2CH_2C_6H_5$	70	165-166	74.64	7.37	3.31	77.67	7.48	3.35
133	*4-ethyl analogue of (114)					72	120 (lit[88].)	Previously charaterised[88]					

Table 19

Spectroscopic data for 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines

Compound	ν_{max} /cm^{-1} NH+OH	δ_H (100 MHz; standard TMS).
114	3400	($CDCl_3$), 7.2-6.7 (5H,m,-CH_2-Ar), 6.4 (1H,s,C8-H), 6.0 (1H,s,C5-H), 3.9 (2H, d,ArCH_2N-), 3.76 (3H,s,C7-OCH_3), 3.3 (3H,s,C6-OCH_3), 3.1 (2H,s,ArCH_2-), 2.0-1.0 (12H*,m,C_5H_{10}+NH+OH).
115	3445	($CDCl_3$) 7.4-6.7 (5H,m,-CH_2-Ar), 6.45 (1H,s,C8-H), 6.0 (1H,s,C5-H), 4.0 (2H, q,OCH_2CH_3,J=7Hz), 3.85 (2H,d,ArCH_2N-), 3.3 (3H,s,OCH_3), 3.05 (2H,s,ArCH_2-), 2.0-1.4 (12H*,m,C_5H_{10}+NH+OH), 1.3 (3H,t,OCH_2CH_3,J=7Hz).
116	3400	($CDCl_3$), 7.2-6.5 (5H,m,-CH_2Ar), 6.4 (1H,s,C8-H), 6.05 (1H,s,C5-H), 3.85 (2H, d,ArCH_2N-), 3.75 (3H,s,OCH_3) 3.45 (2H,m,OCH_2CH_3), 3.05 (2H,s,-CH_2Ar), 2.0-1.2 (12H*,m,C_5H_{10}+NH+OH), 1.1 (3H,t,OCH_2CH_3,J=7Hz).
117	3400	(DMSO), 8.35 (1H,broad s,ArOH)$^{\Phi}$, 7.2-6.5 (5H,m,-CH_2Ar), 6.30 (1H,s,C8-H), 5.95 (1H,s,C5-H), 4.3 (1H,s,OH)$^{\Phi}$, 3.7 (2H,s,ArCH_2N-), 3.15 (3H,s,OCH_3), 3.15-2.8 (2H,ABq,ArCH_2-,J_{AB}=13Hz), 2.3-1.0 (11H*,m,C_5H_{10}+NH).
118	3400	(DMSO), 8.0 (1H,s,Ar-OH)$^{\Phi}$, 7.2-6.6 (5H,m,CH_2-Ar), 6.45 (1H,s,C8-H), 5.15 (1H,s,C5-H), 4.3 (1H,s,OH)$^{\Phi}$, 3.70 (5H,s,OCH_3+ArCH_2N-), 3.20-2.80 (2H, ABq,ArCH_2,J_{AB}=13Hz), 2.10-1.0 (11H*,m,C_5H_{10}+NH).

Table 19 (continued)

Spectroscopic data for 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines

Compound	ν_{max} /cm^{-1} NH+OH	δ_H (100 MHz; standard TMS).
119	3420	(DMSO), 8.25 (1H,s,Ar-O<u>H</u>)$^{\Phi}$, 7.0-6.6 (5H,m,-CH_2-Ar), 6.28 (1H,s,C8-H), 5.94 (1H,s,C5-H), 4.25 (1H,s,OH)$^{\Phi}$, 3.65 (2H,s,Ar<u>CH_2</u>N-), 3.3 (2H,m,O<u>CH_2</u>CH_3), 3.15-2.8 (2H,ABq,-<u>CH_2</u>Ar,J_{AB}=13Hz), 2.0-1.2 (11H*,m,C_5H_{10}+NH), 1.16-1.0 (3H,t, OCH_2<u>CH_3</u>,J=7Hz).
120	3400	(DMSO), 8.20 (1h,s,ArOH)$^{\Phi}$, 7.25-6.50 (5H,m,-CH_2-<u>Ar</u>), 6.42 (1H,s,C8-H), 6.12 (1H,s,C5-H), 4.28 (1H,s,OH)$^{\Phi}$, 3.9-3.75 (2H,q,O<u>CH_2</u>CH_3,J=7Hz), 3.70 (2H,d, $ArCH_2$N-), 3.15-2.78 (2H,ABq,Ar<u>CH_2</u>-,J_{AB}=12Hz), 2.0-1.14 (11H*,m,C_5H_{10}+NH), 1.25 (3H,t,OCH_2<u>CH_3</u>,J=7Hz).
121	3400	($CDCl_3$) 7.40-6.7 (10H,m,2 x -CH_2<u>Ar</u>), 6.4 (1H,s,C8-H), 5.98 (1H,s,C5-H), 3.88 (2H,s,Ar<u>CH_2</u>-N-), 3.80 (3H,s,C7-OCH_3), 3.32 (5H,s,C6-OCH_3+-<u>CH_2</u>Ar), 3.3-2.80 (2H,ABq,C3-<u>CH_2</u>Ar,J_{AB}=12Hz), 1.6 (2H,broad s,NH+OH)$^{\Phi}$, 0.96 (3H,s,CH_3).
122	3410	($CDCl_3$), 7.38-6.60 (10H,m,2 x -CH_2<u>Ar</u>), 6.38 (1H,s,C8-H), 5.92 (1H,s,C5-H), 4.06-3.84 (2H,q,O<u>CH_2</u>CH_3,J=7Hz), 3.78 (2H,s,Ar<u>CH_2</u>-N-), 3.28 (5H,s,OCH_3+-<u>CH_2</u>Ar), 3.26-2.80 (2H,ABq,C3-<u>CH_2</u>Ar,J_{AB}=12Hz), 1.62 (2H,broad s,NH+OH)$^{\Phi}$, 1.36-1.20 (3H, t,$OCH_2$$CH_3$,J=7Hz), 0.96 (3H,s,$CH_3$).

Table 19 (continued)

Spectroscopic data for 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines

Compound	ν_{max} /cm^{-1} NH+OH	δ_H (100 MHz; standard TMS).
123	3450	($CDCl_3$), 7.4-6.8 (10H,m,2 x -CH_2Ar), 6.62 (1H,s,C8-H), 6.04 (1H,s,C5-HO, 4.20-3.90 (2H,q,C3-CH_2Ar,J_{AB}=16Hz), 3.40 (3H,s,OCH_3), 3.20 (2H,s,ArCH_2-N-), 2.78 (2H,s,-CH_2Ar), 1.90 (2H,broad s,NH+OH)$^{\Phi}$, 1.16 (3H,s,CH_3).
124	3400	($CDCl_3$), 7.40-6.80 (10H,m,2 x-CH_2Ar), 6.63 (1H,s,C8-H), 6.038 (1H,s,C5-H), 4.20-3.70 (2H,q,C3-CH_2Ar,J_{AB}=16Hz), 3.80 (3H,s,OCH_3), 3.75 (2H,s,ArCH_2-N-), 3.5-3.05 (4H,m,OCH_2CH_3+C4-CH_2Ar), 2.96-2.48 (2H,ABq,C3-CH_2Ar,J_{AB}=16Hz), 2.00 (1H,broad s,NH)$^{\Phi}$, 1.18-1.02 (3H,t,OCH_2CH_3,J=8Hz), 0.98 (3H,s,CH_3).
125	3420	(DMSO), 8.26-8.10 (1H,broad s,ArOH)$^{\Phi}$, 7.42-6.75 (10H,m,2 x -CH_2Ar), 6.44 (1H, s,C8-H), 5.90 (1H,s,C5-H), 4.20-3.92 (2H,ABq,C3-CH_2Ar,J_{AB}=16Hz), 3.80 (5H,OCH_3 +ArCH_2-N-), 2.84 (2H,s,-CH_2Ar), 1.85 (2H,broad s,NH+OH)$^{\Phi}$, 1.10 (3H,s,CH_3).
126	3400	(DMSO), 8.28 (1H,s,ArOH)$^{\Phi}$, 7.30-6.65 (10H,m,2 x CH_2Ar), 6.40 (1H,s,C8-H), 6.05 (1H,s,C5-H), 4.60 (1H,s,OH)$^{\Phi}$, 3.67 (2H,s,ArCH_2-N-), 3.45-3.00 (4H,m, OCH_2CH_3+C4CH_2Ar), 2.98-2.46 (2H,ABq,C3CH_2Ar,J_{AB}=16Hz), 2.08 (1H,broad s,NH)$^{\Phi}$, 1.16-1.0 (3H,t,OCH_2CH_3,J=7Hz), 0.92 (3H,s,CH_3).

Table 19 (continued)

Spectroscopic data for 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines

Compound	ν_{max} /cm^{-1} NH+OH	δ_H (100 MHz; standard TMS).
127	3450	(DMSO), 7.32-6.68 (10H,m,-CH_2Ar+CH_2CH_2Ar), 6.46 (1H,s,C8-H), 5.90 (1H,s,C5-H), 4.46 (1H,s,OH)$^{\Phi}$, 3.84 (2H,s,ArCH_2-N-), 3.60 (3H,s,C7OCH_3), 3.11 (2H,s,-CH_2-Ar), 3.08 (3H,s,C6OCH_3), 2.80-2.30 (2H,m,-CH_2CH_2Ar), 2.0-1.4 (2H,m,-CH_2CH_2Ar), 1.24 (3H,s,CH_3).
128	3360	($CDCl_3$), 7.3-6.6 (10H,m,-CH_2Ar+-CH_2CH_2Ar), 6.36 (1H,s,C8-H), 5.94 (1H,s,C5-H), 4.08-3.80 (2H,q,OCH_2CH_3,J=8Hz), 3.76 (2H,s,ArCH_2-N-), 3.28 (3H,s,OCH_3), 3.1 (2H,s,-CH_2Ar), 2.80-2.50 (2H,m,-CH_2CH_2Ar), 1.88-1.68 (2H,m,-CH_2CH_2Ar), 1.64 (2H,s,NH+OH)$^{\Phi}$, 1.35 (3H,s,CH_3), 1.30-1.12 (3H,t,OCH_2CH_3,J=8Hz).
129	3440	(DMSO), 8.7-8.5 (1H,broad s,ArOH)$^{\Phi}$, 7.40-6.70 (10H,m,-CH_2-Ar+-CH_2CH_2Ar), 6.39 (1H,s,C8-H), 5.96 (1H,s,C5-H), 2.44 (1H,s,OH)$^{\Phi}$, 3.80 (2H,s,ArCH_2N-), 3.12 (5H,s,OCH_3+-CH_2-Ar), 2.80-2.50 (2H,m,-CH_2CH_2Ar), 1.90-1.20 (2H,m, -CH_2CH_2Ar), 1.25 (3H,s,CH_3).

Table 19 (continued)

Spectroscopic data for 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines

Compound	ν_{max} /cm^{-1} NH+OH	δ_H (100 MHz; standard TMS).
130	3400	($CDCl_3$), 7.30-6.70 (10H,m,-CH_2<u>Ar</u>+-CH_2CH_2<u>Ar</u>), 6.44 (1H,s,C8-H), 6.08 (1H,s,C5-H), 3.80 (5H,s,OCH_3+Ar<u>CH_2</u>NH-), 3.64-3.30 (2H,m,O<u>CH_2</u>CH_3), 3.13 (2H,s,-<u>CH_2</u>-Ar), 2.90-2.60 (2H,m,-CH_2<u>CH_2</u>Ar), 1.90-1.45 (2H,m,-<u>CH_2</u>CH_2Ar), 1.7 (2H,s,NH+OH)$^{\Phi}$, 1.36 (3H,s,CH_3), 1.30-1.12 (3H,t,OCH_2<u>CH_3</u>,J=7Hz).
131	3410	(DMSO), 8.30-8.20 (1H,broad s,ArOH)$^{\Phi}$, 7.42-6.80 (10H,m,-CH_2<u>Ar</u>?CH_2-CH_2Ar), 6.42 (1H,s,C8-H), 6.0 (1H,s,C5-H), 4.38 (1H,s,OH)$^{\Phi}$, 3.80 (5H,s,OCH_3+ArCH_2N-), 2.82-2.54 (2H,m,-CH_2<u>CH_2</u>Ar), 1.62-1.40 (2H,m,-<u>CH_2</u>CH_2Ar) 1.26 (3H,s,CH_3).
132	3460	(DMSO), 8.50-8.25 (1H,s,-Ar<u>OH</u>)$^{\Phi}$, 7.36-6.70 (10H,m,-CH_2<u>Ar</u>.+CH_2-CH_2<u>Ar</u>), 6.38 (1H, s,C8-H), 6.00 (1H,s,C5-H). 4.40 (1H,s,OH)$^{\Phi}$, 3.80 (2H,s,Ar-<u>CH_2</u>-N),3.38-3.0 (4H, m,O<u>CH_2</u>CH_3+Ar-<u>CH_2</u>-N-), 1.80-2.20 (2H,m,-CH_2<u>CH_2</u>Ar), 2.00-1.40)2H,m,-<u>CH_2</u>CH_2Ar), 1.25 (3H,s,CH_3), 1.18-1.0 (3H,t,OCH_2<u>CH_3</u>,J=7Hz).
133	3350	($CDCl_3$), 7.06 (1H,s,C5-H), 6.46 (1H,s,C8-H), 3.86 (6H,s,2 x OCH_3), 3.80 (2H, s,Ar<u>CH_2</u>NH-), 1.85 (2H,q,-<u>CH_2</u>-CH_3,J=7Hz),2.0-1.0 (12H*,m,C_5H_{10}+NH+OH), 0.85 (3H,t,-CH_2<u>CH_3</u>,J=7Hz).

* Reduced to 10 after deuteration.

Φ Disappeared after deuteration.

Table 20

Mass spectral fragmentation of 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines.

Compound		Relative abundancies
114	m/z	367 (M^{+}4.21%), 349 (22.38%), 276 (3.1), 258 (43.12), 151 (5.89), 136 (3.89).
115	m/z	381 (M^{+}2.36%), 214 (35.55), 320 (11.05), 306 (19.18), 290 (4.23), 272 (100), 244 (10.31), 214 (3.13), 193 (68.06), 165 (14.89), 137 (4.31), 136 (1.95), 107 (2.16), 98 (84.37).
116	m/z	381 (M^{+}1.85%), 363 (40.41), 320 (14.15), 306 (17.21), 290 (3.8), 272 (100), 244 (9.81), 214 (2.95), 193 (72.10), 165 (17.13), 137 (8.17), 136 (3.17), 107 (2.19), 98 (87.4).
117	m/z	353 (M^{+}3.47%), 335 (20.69) 278 (13.17), 244 (33.76) 214 (1.40), 165 (69.51), 137 (8.39), 136 (2.45), 98 (100).
118	m/z	353 (M^{+}2.62%), 335 (28.55), 333 (20.07), 278 (17.42), 244 (85.71), 242 (4.52), 237 (2.43), 234 (4.63), 219 (1.28), 214 (2.93), 165 (90.62), 137 (21.18), 136 (6.75), 123 (1.15), 98 (100).
119	m/z	367 (M^{+}2.19%), 349 (20.28), 321 (1.15), 320 (3.93), 276 (4.38), 258 (41.04), 230 (13.12), 179 (76.49), 151 (7.40), 123 (7.43), 98 (100).

Table 20 (continued)

Mass spectral fragmentation of 4-benzyl-4-hydroxy-1,2,3,4-tetrahydrosioquinolines.

Compound		Relative abundancies
120	m/z	367 (M^{+}1.78%), 349 (27.65), 321 (2.18), 320 (8.71), 276 (6.11), 258 (49.10), 230 (13.69), 179 (78.16), 151 (8.39), 123 (10.01), 98 (100).
121	m/z	403 (M^{+}1.21%), 312 (4.22), 294 (1.15), 268 (6.87), 221 (8.02), 220 (14.21), 206 (61.78), 179 (100%), 106 (9.41),137 (20.52), 136 (8.94), 135 (11.97), 134 (98.14), 121 (2.12).
122	m/z	417 (M^{+}0.86%), 399 (0.40), (326 (22.59), 308 (8.60), 280 (2.37), 234 (27.45), 206 (6.72), 193 (93.33), 165 (6.99), 137 (8.52), 134 (100).
123	m/z	389 (M^{+}1.11%), 371 (1.03), 289 (54.09), 280 (51.19), 206 (61.47), 165 (82.98), 137 (6.85), 136 (2.57), 134 (100).
124	m/z	417 (M^{+}0.74%), 399 (1.14), 326 (30.09), 308 (22.97), 280 (3.94), 252 (3.25), 234 (32.12), 206 (7.06), 193 (97.59), 165 (6.02), 137 (7.70), 134 (100).
125	m/z	389 (M^{+}1.87%), 371 (1.61), 289 (55.16), 280 (58.19), 206 (63.47), 165 (80.91), 137 (9.91), 134 (100).

Table 20 (continued)

Mass spectral fragmentation of 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines.

Compound		Relative abundancies
126	m/z	403 (M^+ 0.70%), 312 (0.49), 294 (3.41), 297 (0.31), 266 (0.80), 251. (0.31), 223 (1.34) 206 (1.34), 196 (11.05), 182 (21.65), 167 (18.43), 149 (11.54), 107 (22.91), 91 (100).
127	m/z	417 (M^+ 0.73%), 399 (0.55), 326 (1.33), 308 (13.16), 296 (1.20), 294 (12.29), 267 (9.06), 238 (8.63), 220 (11.33), 203 (1.15), 191 (100), 176 (2.25), 148 (87.86), 136 (3.74), 105 (6.28).
128	m/z	431 (M^+ 1.08%), 413 (0.41), 340 (1.43) 322 (9.44), 308 (8.76), 294 (1.08), 282 (9.90), 235 (3.56), 206 (4.15), 193 (93.49), 189 (4.21), 175 (10.02), 165 (18.70), 159 (5.17), 148 (100), 137 (7.25), 135 (6.87).
129	m/z	403 (M^+ 1.40%), 385 (0.91), 312 (1.60), 294 (37.77), 282 (2.68), 280 (46.85), 264 (2.04), 254 (2.95), 206 (13.66), 202 (6.10), 188 (2.95), 165 (99.66), 148 (100), 137 (13.48), 105 (6.96).
130	m/z	431 (M^+ 0.89%), 340 (1.37), 322 (12.06), 294 (1.79), 282 (7.03), 235 (3.96), 206 (3.60), 193 (100), 175 (1.00), 165 (9.15%), 148 (98.8), 137 (10.47), 135 (2.57).

Table 20 (continued)

Mass spectral fragmentation of 4-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines.

Compound		Relative abundancies
131	m/z	403 (M^+ 0.98%), 385 (1.62), 312 (2.10), 294 (39.87), 282 (4.31), 280 (52.35), 264 (2.64), 254 (4.78), 206 (17.78), 202 (8.99), 188 (96.71), 148 (100), 137 (10.71), 105 (7.11).
132	m/z	417 (M^+ 1.53%), 399 (0.96), 326 (1.38), 308 (30.71), 294 (39.35), 280 (3.32), 266 (1.48), 221 (4.23), 220 (7.47), 179 (75.17), 175 (2.83), 151 (8.51), 148 (100), 147 (2.58), 123 (7.48), 105 (6.13).
133	m/z	305 (M^+ 2.47%), 287 (76.10), 276 (1.42), 275 (2.81), 272 (14.92), 258 (83.25), 245 (7.40), 244 (38.21), 242 (9.81), 229.73 (10.02), 216 (4.35), 208 (13.04), 206 (10.92), 205 (11.38), 191 (8.02), 179 (57.69), 151 (13.94), 136 (3.08).

4.4 Selective O-dealkylation of 6,7-Dialkoxy-2,3--dihydro-4(1H)-isoquinolones. General method.

The 6,7-dialkoxy-2,3-dihydro-4(1H)-isoquinolone (3 g) was added carefully to concentrated sulphuric acid (98%, 30 ml) at 0° with continuous stirring. When dissolution was complete, the temperature was raised to room temperature or 50° and stirring continued for a further four hours. In the case of dealkylation at -10°, this temperature was maintained throughout the procedure.

The solution was then poured onto crushed ice and stirred for 45 minutes. The diluted mixture was basified with 5M sodium hydroxide, ice being added from time to time to prevent excessive rise in temperature.

The alkaline solution was extracted with chloroform (5 x 200 ml). The combined extracts were dried using magnesium sulphate, filtered and evaporated to dryness under reduced pressure to give product. (Table 21)

The extracted aqueous solution was reacidified with concentrated hydrochloric acid, basified with potassium hydrogen carbonate and extracted with chloroform (8 x 100 ml). After drying the combined extracts ($MgSO_4$), removal of solvent under reduced pressure, gave the phenolic product. (Table 21)

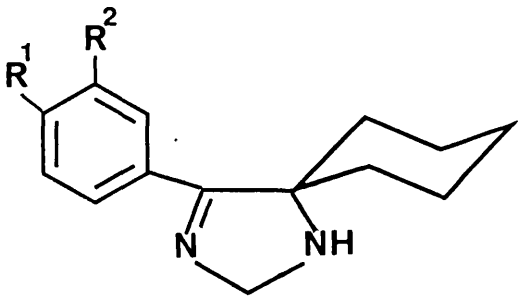
Table 21

Selective O-dealkylation of 6,7-Dialkoxy-2,3-dihydro-4(1H)-isoquinolones

Isoquinolinone	Phenolic product	m.p.°C	Yield % of Phenolic product at			Yield % of Dialkoxyisoquinolone recovered at		
			-10°	R.T.	50°	-10°	R.T.	50°
79	84	208-209	0	20	78	78	61	3
81	80	161-162	3	29	26	82	39	2
83	84	208-209	0	43	85	76	27	0
89	134	162-163	0	21	79	87	59	4
90	84	208-209	0	20	80	88	55	3

Table 22

3-Imidazolines



Compound	R^1	R^2	From nitrile	% yield at -10°C	R.T.	50°
135	CH_3O	H	74	87	82	70
136	HO	H	74	2	6	20
137	CH_3CH_2O	H	75	80	60	10
136	OH	H	75	8	20	82
138	CH_3CH_2O	CH_3	76	82	58	8
139	OH	CH_3	76	9	25	85

Table 23

3-Imidazolines

Compound	Formula	m.p.	Recrystallisation solvent pet-ether (60-80°)/ethylacetate	Found %			Required %		
				C	H	N	C	H	N
135	$C_{15}H_{20}N_2O$	90-91 (lit[66] 92)	1:0	Previously characterised[66]					
136	$C_{14}H_{18}N_2O$	197-198	1:1	73.48	7.92	12.48	73.01	7.87	12.16
137	$C_{16}H_{22}N_2O$	82-83	1:0	74.26	8.56	10.73	74.38	8.58	10.84
138	$C_{17}H_{25}N_2O$	108-109	1:0	75.03	9.02	10.36	74.96	8.88	10.28
139	$C_{14}H_{18}N_2O$	165-166	2:1	74.01	8.44	11.75	73.74	8.25	11.46

Table 24

Spectroscopic data for 3-Imidazolines.

Compound	ν_{max} /cm^{-1} NH	OH	δ_H (100 MHz; standard TMS).
135	3340		($CDCl_3$), 7.75-6.8 (4H, AA^1XX^1, ArH), 4.75 (2H,s,=N-CH_2-NH), 3.75 (3H,s,OCH_3) 2.3 (1H,s,NH), 1.92-1.5 (10H,m,C_5H_{10}).
136	3345	3580	(DMSO), 7.72-6.84 (4H, AA^1XX^1, ArH), 4.58 (2H,s,=N-CH_2), 2.0-1.4 (12H*,m, C_5H_{10}+NH+OH).
137	3310		($CDCl_3$), 7.80-6.80 (4H, AA^1XX^1, ArH), 4.76 (2H,s,=N-CH_2-NH), 4.12-3.92 (2H,q, OCH_2CH_3, J=7Hz), 2.48 (1H,s,NH)$^{\text{Ⓓ}}$, 2.08-1.56 (10H,m,C_5H_{10}), 1.44-1.28 (3H,t, OCH_2CH_3, J=7Hz).
138	3300		($CDCl_3$), 7.58-6.69 (3H,m,C_6H_3), 4.72 (2H,s,=N-CH_2-NH), 4.1-3.89 (2H,q, OCH_2CH_3, J-7Hz), 2.25 (3H,s,CH_3), 1.90 (1H,s,NH)$^{\text{Ⓓ}}$, 1.80-1.52 (10H,m,C_5H_{10}), 1.46-1.32 (3H,t,OCH_2CH_3, J=7Hz).
139	3350	3600	(DMSO), 8.25 (1H,s,OH)$^{\text{Ⓓ}}$, 7.50-7.30 (3H,m,C_6H_3), 4.57 (2H,s,=N-CH_2NH), 2.15 (3H,s,CH_3), 2.0-1.2 (11H*,m,C_5H_{10}+NH).

Ⓓ Disappeared after deuteration.

* Reduced to 10 after deuteration.

Table 25

Mass spectral fragmentation of 3-Imidazolines. (Electron impact)

Compound		Relative abundancies
135	m/z	244 (M^+ 2.76%), 243 (11.21), 201 (43.75), 187 (7.89), 173 (2.16) 147 (9.11), 133 (7.23), 111 (100), 97 (7.18).
136	m/z	230 (M^+ 4.33%), 229 (8.20), 187 (49.88), 173 (6.02), 133 (6.36), 119 (4.27), 111 (100), 97 (o.59%), 96 (5.36).
137	m/z	258 (M^+ 1.82%), 257 (4.23), 229 (1.53), 215 (25.87), 187 (1.99), 173 (2.87), 161 (2.10), 133 (2.24), 119 (3.83), 111 (100), 96 (4.99).
138	m/z	272 (M^+ 1.58%), 271 (3.11%), 229 (18.26), 200 (2.41), 187 (2.28), 175 (1.61), 133 (2.72), 111 (100), 96 (5.68).
139	m/z	244 (M^+ 2.36%), 243 (5.08), 201 (42.04), 187 (4.57), 173 (1.31), 147 (4.72), 133 (2.93), 111 (100), 96 (5.92).

Dibenzylamine hydrochloride

This was prepared by the procedure described by G Grethe and co-workers[48].

A solution of 3,4-dimethoxybenzaldehyde (49.8 g, 0.3 mol) and benzylamine (32.1 g, 0.3 mol) in dry toluene (125 ml) was refluxed until no more water was collected in a Dean-Stark water trap (6 hours).

The toluene was removed under reduced pressure, the residue was dissolved in 95% ethanol (250 ml) and sodium borohydride (7.6 g, 0.3 mol) was added to the stirred mixture in small portions. After addition was completed, stirring was continued for further 2 hours.

The solvent was removed under vacuum and water (75 ml) was added to the residue. After the mixture was warmed slightly for a short time, the insoluble oil was extracted with ether (3 x 100 ml).

The combined ether extracts were dried with magnesium sulphate and filtered. Removal of solvent under reduced pressure gave an oil which was redissolved in dry ether. Addition of etheral hydrogen chloride gave the crude dibenzylamine hydrochloride, which was recrystallised from ethanol to give white needles (71 g, 80°), m.p. 185-187° (lit[48] 184-186°).

Ethyl-α-aminoisobutyrate hydrochloride

This compound was prepared by the method of Fischer[114] for the preparation of similar compounds.

The α-aminoisobutyric acid (20 g, 0.19 mol) was suspended in absolute ethanol (100 ml) and dry hydrogen chloride gas introduced without cooling for 20 minutes. The solution was heated on a boiling water bath for a further ten minutes and then cooled in ice. The copious precipitate of the aminoester hydrochloride was isolated by filtration, washed with cold ethanol:ether (1:1), dried and recrystallised from ethanol to yield ethyl-α-aminoisobutyrate hydrochloride as white needles (23 g, 70%), m.p. 160-161° (lit[115] 155-157°).

Ethyl-1-aminocyclohexane carboxylate hydrochloride

This was prepared by the method described by Piper and co-workers[116]

1-aminocyclohexane-1-carboxylic acid (50 g, 0.32 ml) was added to absolute ethanol (300 ml) and hydrogen chloride gas was introduced into the solution until saturation (9.5 hours) and the resultant mixture was refluxed for 6 hours and then cooled to room temperature.

The excess ethanol (50 ml) was evaporated under reduced pressure. The mixture was cooled (ice-methanol bath). The solid hydrochloride formed as thick sluggish white material, which was filtered washed with ether, dried and recrystallised from ethanol-ether (1:1) to give white needles of ethyl-1-aminocyclohexane carboxylate hydrochloride (53 g, 72%), m.p. 192-193 (lit[117] 194-195°).

4.5 N-(3,4-dimethoxybenzyl) glycine ethyl esters

General method

Method A[48]

A mixture of benzylamine (0.235 mol), ethylchloroacetate (0.247 mol), anhydrous sodium carbonate (37.4 g) and toluene (250 ml) was stirred and refluxed overnight.

After cooling and removal of the salts by filtration, the filtrate was evaporated to dryness under reduced pressure. The residue was covered with ether and was allowed to stand for one hour at room temperature. A small quantity of undissolved material was removed by filtration and discarded.

The removal of ether under reduced pressure gave an oil, which was dissolved in dry ether (250 ml). The addition of etheral hydrogen chloride resulted in precepitation of crystalline hydrochloride, which was filtered, dried and recrystallised from acetone: ether (1:1) to give white needles of the appropriate N-(3,4-dimethoxybenzyl) glycine ethyl ester. (Table 26)

Method B

A solution of 3,4-dimethoxybenzaldehyde (0.2 ml) and the amino ethyl ester (0.2 mol) in dry toluene (100 ml) was refluxed until no more water was collected in a Dean-Stark water trap (6 hours).

The toluene was removed under reduced pressure, the residue was dissolved in methanol (250 ml) and hydrogenated over 5% palladium on charcoal (3.0 g) at room temperature and 60 p.s.i. until the hydrogen untake ceased (4 hours).

The catalyst was removed by filtration and washed thoroughly with warm methanol. The combined filtrate and washings were evaporated under reduced pressure and the residue was dissolved in dry ether. The addition of etheral hydrogen chloride resulted in precipitation of the glycine ester hydrochloride. Purification was effected by recrystallisation from ethylacetate/methanol (9:1). (Table 26)

4.6 Cyclisation of glycine ethyl esters

General procedure[48]

To sulphuric acid (80% by weight, 100 ml) was cautiously added the glycine ethyl ester hydrochloride (0.05 mol), with external ice cooling.

The resulting solution was kept at -10°C*, room temperature* and 100°C for 4.5 hours, cooled to room temperature, and added slowly with stirring to ice cold 6M sodium hydroxide (500 ml). The alkaline solution was extracted with chloroform (5 x 200 ml). The combined extracts were dried using magnesium sulphate, filtered, and evaporated to dryness under reduced pressure to give the 2,3-dihydro-4--(1H)-isoquinolinones, which were isolated as crystalline hydrochlorides.

The extracted aqueous solution was reacidified with concentrated hydrochloric acid, basified with potassium hydrogen carbonate and extracted with chloroform (8 x 100 ml). Drying the combined extracts using magnesium sulphate, filtration and removal of solvent gave the phenolic product.

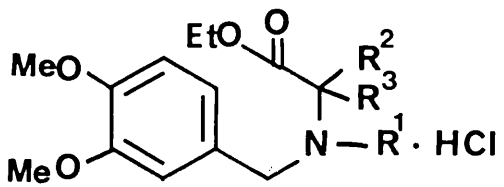
Thus cyclisation of benzylglycine ethyl ester (157) gave 2-benzyl-2,3-dihydro-6,7-dimethoxy-4(1H)-isoquinolinone hydrochloride (161) (table 28), which was recrystallised from methanol to give yellow neeedles (9%) m.p. 218-219° (lit[48] 216-217°) and a phenolic product, which was recrystallised from ethylacetate to give yellow needles of 2-benzyl-2,3-dihydro-7-hydroxy-6-methoxy-4(1H)-isoquinolinone (163) (18%), m.p. 206-209° (lit[91] 208-218°) (table 28.)

(* No product could be isolated at these temperatures).

The glycine ethyl esters (158,159 and 160) failed to cyclise at any of the chosen temperatures.

Table 26

Glycine ethyl ester derivatives



Compd	Formula	R^1	R^2	R^3	Method of prep	yield (%)	m.p. (°C)	Found % C	Found % H	Found % N	Reqiured % C	Reqiured % H	Reqiured % N
140	$C_{20}H_{26}NO_4Cl$	$CH_2C_6H_5$	H	H	A	80	138-139 (lit[48] 141 -141)	Previously characterised[48]					
141	$C_{13}H_{20}NO_4Cl$	H	H	H	A	75	123-124	54.01	7.04	4.71	53.89	6.96	4.83
142	$C_{15}H_{28}NO_4Cl$	H	CH^3	CH_3	B	83	164-165	56.83	7.86	4.00	65.69	7.61	4.41
143	$C_{18}H_{28}NO_4Cl$	H	$-CH_2(CH_2)_3CH_2-$		B	85	190-191	60.72	8.12	3.73	60.41	7.89	3.91

Table 27

Spectroscopic data for glycine ethyl ester derivatives (free bases)

Compound	ν_{max} /cm^{-1} NH	CO	δ_H (100 MHz; standard TMS).
140	3340	1730	($CDCl_3$), 7.40-6.68 (8H,m,C_6H_3+CH_2Ar), 4.24-4.00 (2H,q,O$CH_2$$CH_3$,J=7Hz), 3.84 (2H,s,Ar-$CH_2$-n-), 3.80 (6H,s,2 x O$CH_3$), 3.73 (2H,s,-N-$CH_2$-Ar), 3.26 (2H,s,-$CH_2$-CO-), 1.27-1.13 (3H,t,O$CH_2$$CH_3$,J=7Hz).
141	3320	1725	($CDCl_3$), 6.94-6.8 (3H,m,C_6H_3), 4.28-4.04 (2H,q,O$CH_2$$CH_3$,J=7Hz), 3.84 (6H,2 x s, 2 x OCH_3), 3.72 (2H,s,Ar-CH_2-NH-), 3.36 (2H,s,-N-CH_2-), 2.04 (1H,s,NH)$^{\Phi}$, 1.29-1.14 (3H,t,O$CH_2$$CH_3$,J=7Hz).
142	3300	1735	($CDCl_3$), 6.87-6.70 (3H,m,C_6H_3), 4.28-4.05 (2H,q,O$CH_2$$CH_3$,J=7Hz), 3.90-3.80 (6H, 2 x s,2 x OCH_3), 3.52 (2H,s,ArCH_2-NH-), 2.24-2.00 (1H,Broad s,NH)$^{\Phi}$, 1.35 (6H, s, 2 x CH_3), 1.34-1.200 (3H,t,O$CH_2$$CH_3$,J=7Hz).
143	3360	1740	($CDCl_3$), 6.92-6.76 (3H,m,C_6H_3), 4.32-4.08 (2H,q,O$CH_2$$CH_3$,J=7Hz), 3.96-3.70 (6H,2s,2 x OCH_3), 2.52 (2H,s,ArCH_2-NH-), 1.60 (1H,s,NH)$^{\Phi}$, 2.0-1.40 (10H,m,C_5H_{10}), 1.36-1.20 (3H,t,O$CH_2$$CH_3$,J=7Hz).

$^{\Phi}$ Disappeared after deuteration.

Table 28

Mass spectral fragmentation of glycine ethyl ester derivatives. (Electron impact)

Compound		Relative abundancies
141	m/z	253 (M^{+} 4.23%), 166 (35.15), 151 (100), 136 (2.55), 124 (1.23), 107 (6.07).
142	m/z	281 (M^{+} 0.26%), 208 (19.87), 166 (7.54), 151 (100), 136 (1.03), 107 (4.98).
143	m/z	321 (M^{+} 30.16%), 248 (21.66), 166 (7.65), 151 (100), 124 (3.40), 108 (1.70), 107 (3.71), 106 (2.32).

Table 29

Spectroscopic data for 2-benzyl-2,3-dihydro-4(1H)-isoquinolones

Compound	ν_{max} /cm^{-1} NH(OH)	CO	δ_H (100 MHz; standard TMS).
144	2400 broad	1660	(DMSO), 7,65 (1H,s,C5-H), 7.50-7.30 (5H,m,-CH_2Ar), 6.88 (1H,s,C8-H), 4.00-3.92 (5H,broad s,OCH_3+CH_2-N-), 3.84 (3H,s,OCH_3), 3.78-3.68 (4H,s,broad s,CH_2-CO+-CH_2-N-CH_2).
145	(3560)	1620	(DMSO), 10.40-9.80 (1H,broad s,ArOH)Φ, 7.36 (7.16**,1H,s,C5-H), 7.34-7.28 (5H,m,-CH_2Ar), 6.70 (6.22**,1H,s,C8-H), 3.80 (3.70**,3H, s,OCH_3), 3.66 (2H,s,-CH_2-N-)m 3.40 (2H,s,-CH_2-N-CH_2), 3.20 (2H,s, CH_2-CO).

** After addition of 30% NaoD in D_2O.

Φ Disappeared after deuteration.

Table 30

Mass spectral fragmentation of 2-benzyl-2,3-dihydro-4(1H)-isoquinolones. (Electron impact)

Compound		Relative abundancies
144*	m/z	297 (11.73%), 283 (4.91), 268 (5.96), 206 (100), 192 (33.54), 178 (15.21), 150 (24.07), 136 (11.84).
145	m/z	283 (M^+ 13.03%), 282 (4.10%), 255 (4.10%), 192 (100%), 164 (20.67%), 149 (2.12%), 137 (8.17%), 136 (22.64%), 121 (1.74), 120 (1.03%).

* Hydrochloride.

PART V

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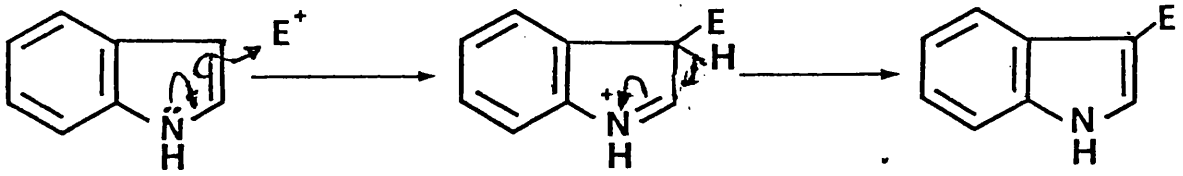
SUPPLEMENT

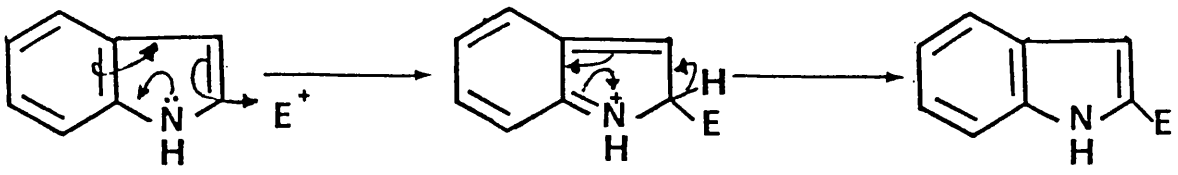
Spirocyclic intermediates

The formation of the spirocyclic-intermediates is now accepted in many different types of organic reactions involving carbocations, carbanions and free radical intermediates.

The occurrence of 3-spirocyclic intermediates in indole chemistry is well documented.[119-129] Essentially, the indole ring is susceptible to electrophilic substitution at C-3 (Scheme 74), although substitution at C-2 also occurs (Scheme 75), The latter, however, is the less favoured as it involves disruption of the aromatic character of the benzene ring and it is considered that many such substitutions at this position are indirect.



Scheme 74

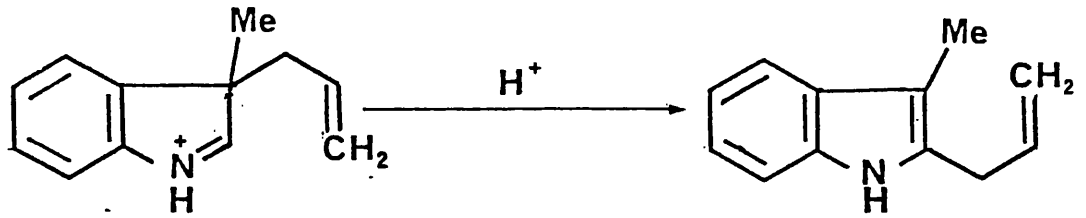


Scheme 75

E^+ = Electrophile

Thus although electrophilic substitution of 3-substituted indóles yields 2,3-disubstituted products, there is evidence that in many cases initial attack occurs at the more susceptible 3-position to yield the 3,3-disubstituted indolenine (146) which then undergoes a Wagner-Meerwein type of rearrangement involving migration of one of the 3-substituents to the 2-position.

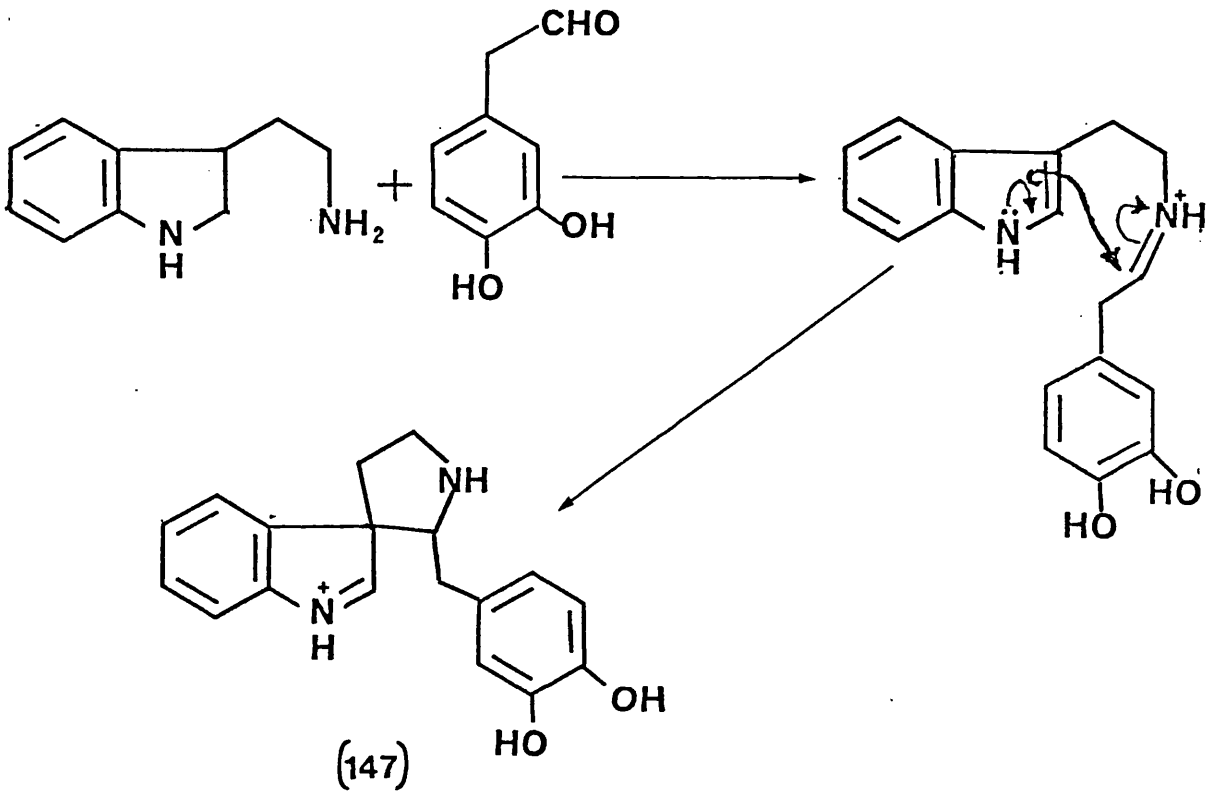
The group that participates in this shift is determined by the relative migratory aptitudes. For example an electrophilic substitution in which the incoming group (Me) caused the migration of the more labile substituent already present (i.e. allyl) into the 2-position and gave 2-allyl-3-methyl indole (Scheme 76) upon treatment with dilute acid.[121]



(146)

Scheme 76

The presence of the spirocylic-intermediate (147) in the electrophilic substitution reactions of indoles was first postulated by Woodward[120] in 1948, while studying the biosynthesis of strychnos alkaloids (Scheme 77).



(147)

Scheme 77

Since the first report by Woodward[120], there has been a substantial number of reports in the literature in support of the spiroindolenine mechanism stemming from investigations of the electrophilic reactivity of the 2,3-indole double bond.

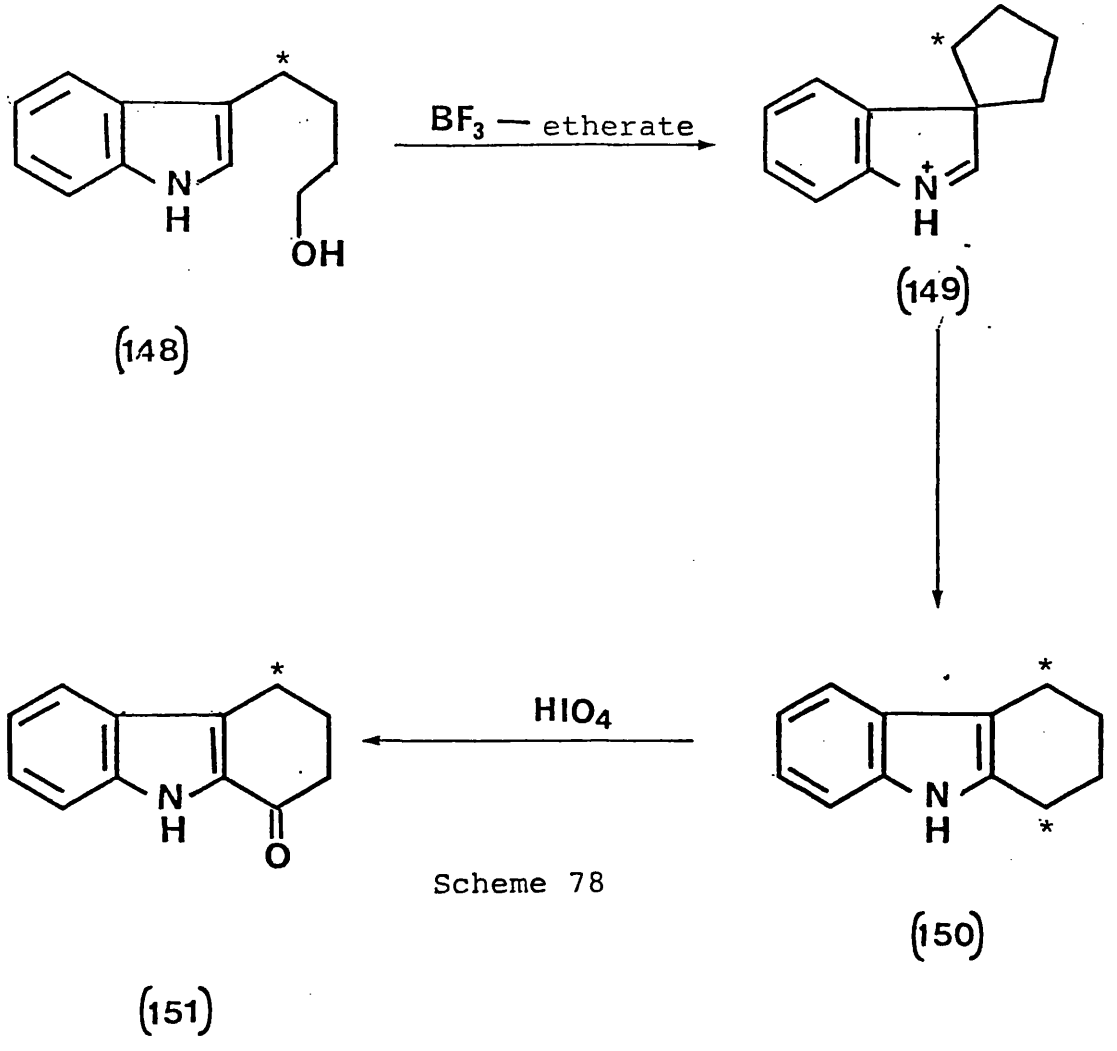
Cyclisation of indolylbutanols

Jackson and Smith[122,124] have reported that when 4-(3-indoyl)butan-1-ol (148) containing tritium in the 4-position was treated with boron trifluoride-etherate with brief heating, it gave the tetrahydro-carbazole (150).

Oxidation of this product with periodic acid has been shown to

yield 1-oxo-tetrahydrocarbazole (151, Scheme 78), which contained only half the radioactivity of the tetrahydrocarbazole (150).

This led Jackson and Smith to conclude that the cyclised product had tritium label distributed equally at the 1- and 4-positions and hence postulating that this scrambling could have only resulted through the spirocyclic-intermediate (149, Scheme 78).



(148) (149) (150) (151)

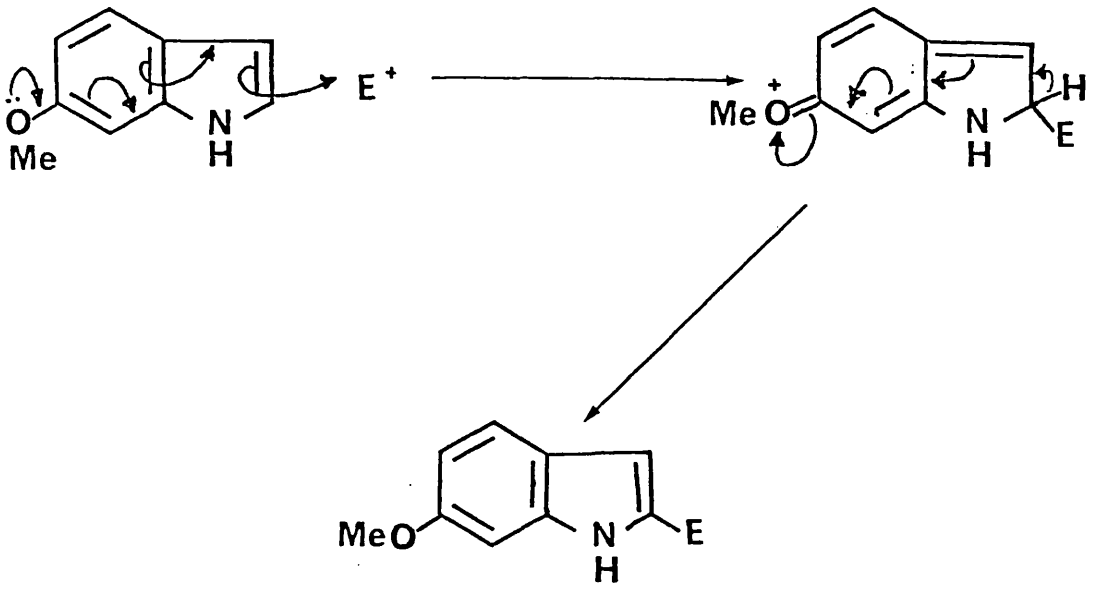
Scheme 78

* = tritium labelled

The influence of electron donating groups on the course of cyclisation

The presence of electron donating groups (e.g. methoxys) at C-6 and C-4 of the indole should facilitate direct substitution of the

indole ring at the 2-position. For example the methoxy group at C-6 may donate electrons to stabilise the intermediate (Scheme 79).



Scheme 79

In a view of this, Jackson and co-workers[127,128,129] studied the effect of the methoxy groups on the course of cyclisation of the indolylbutanols, by examining the boron trifluoride-ether catalysed cyclisation of the 6-methoxy indolybutanol (152) with tritium labelling at the methylene group adjacent to the hydroxyl group.

The resulting mixture of the tritiated 7-methoxy-tetrahydrocarbazoles (154,R=OMe) was isolated by chromatography and crystallised to constant activity. These products were then oxidised with periodic acid to the 1-oxo-derivative to establish the amount of activities at the 1- and 4-positions in the tetrahydrocarbazoles.

However, two products were isolated, the 1-oxo-6-iodo-derivative (156) and the iodo-oxo-amide (157) in 9 and 40% yields respectively

(Scheme 80).

These results were markedly different from the periodic acid oxidiation of the inactivated tetrahydrocarbazole (154, R=H, Scheme 80), which itself afforded a 62% yield of the 1-oxo-derivative (155).

The formation of the iodo-oxo-amide was postulated to be due to the increased activation of the 2,3-double bond in the indole nucleus, caused by the methoxy group.

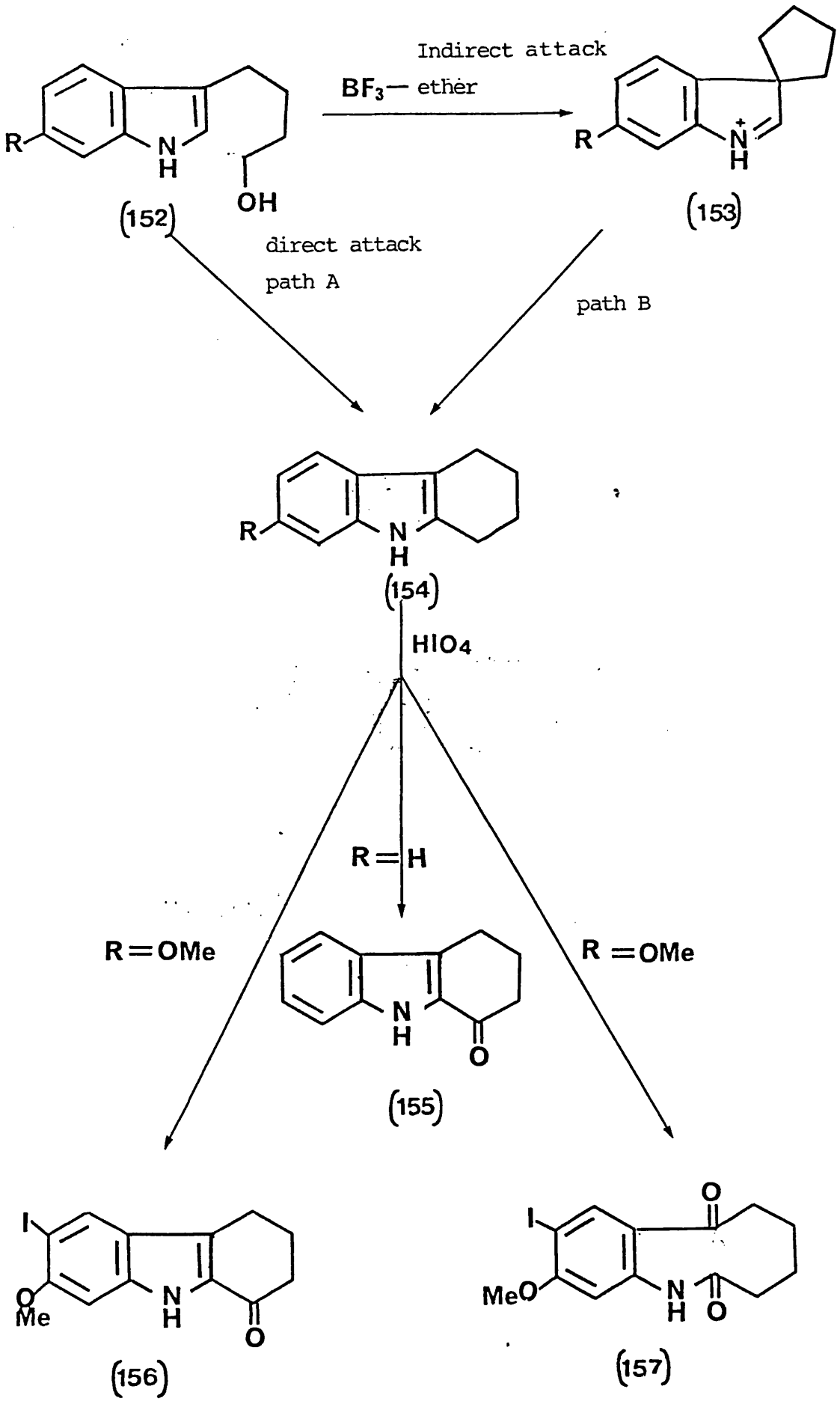
The activity of the iodo-oxo-derivative (156) was found to be 48% of that parent tetrahydrocarbazole (154, R=OMe). This led Jackson and co-workers to suggest that two reaction pathways occurred during the cyclisation reaction, 4.5% by direct substitution at the 2-position (path A, Scheme 80) and 95.5% by the indirect route (path B).

However, owing to the difficulties in obtaining good yields of the 1-oxo-compound (from tritium labelled 6-methoxyindolylbutanol), Jackson and co-workers made use of deuterium for labelling.

Furthermore the authors found that treatment of 7-methoxy tetrahydrocarbazole (160) with sodium metaperiodate resulted in a good yield of the oxo-amide (166 R^1=OMe,R^2=R^3=H).

The ^{1}H n.m.r. spectrum of this product showed significant difference in the resonances of the two methylene protons neighbouring the two carbonyl groups (whereas in the parent tetrahydrocarbazole the 1- and 4-methylene proton resonances were superimposed on one another).

Thus methoxyindolylbutanol (152) labelled with deuterium in the methylene group next to the hydroxy function was cyclised with boron trifluoride-ether at 80°. After isolation by chromatography and oxidation of the deuteriotetrahydrocarbazoles with sodium metaperiodate, the deuteriated amides (166, R^1=OMe,R^2=R^3=H) were obtained. The percentage of deuterium in each of the two appropriate


Indirect attack
BF3— ether
R
N
H
OH
(152)
(153)
direct attack
path A
path B
(154)
HIO4
R=H
R=OMe
R=OMe
(155)
I
O
Me
(156)
MeO
(157)

Scheme 80

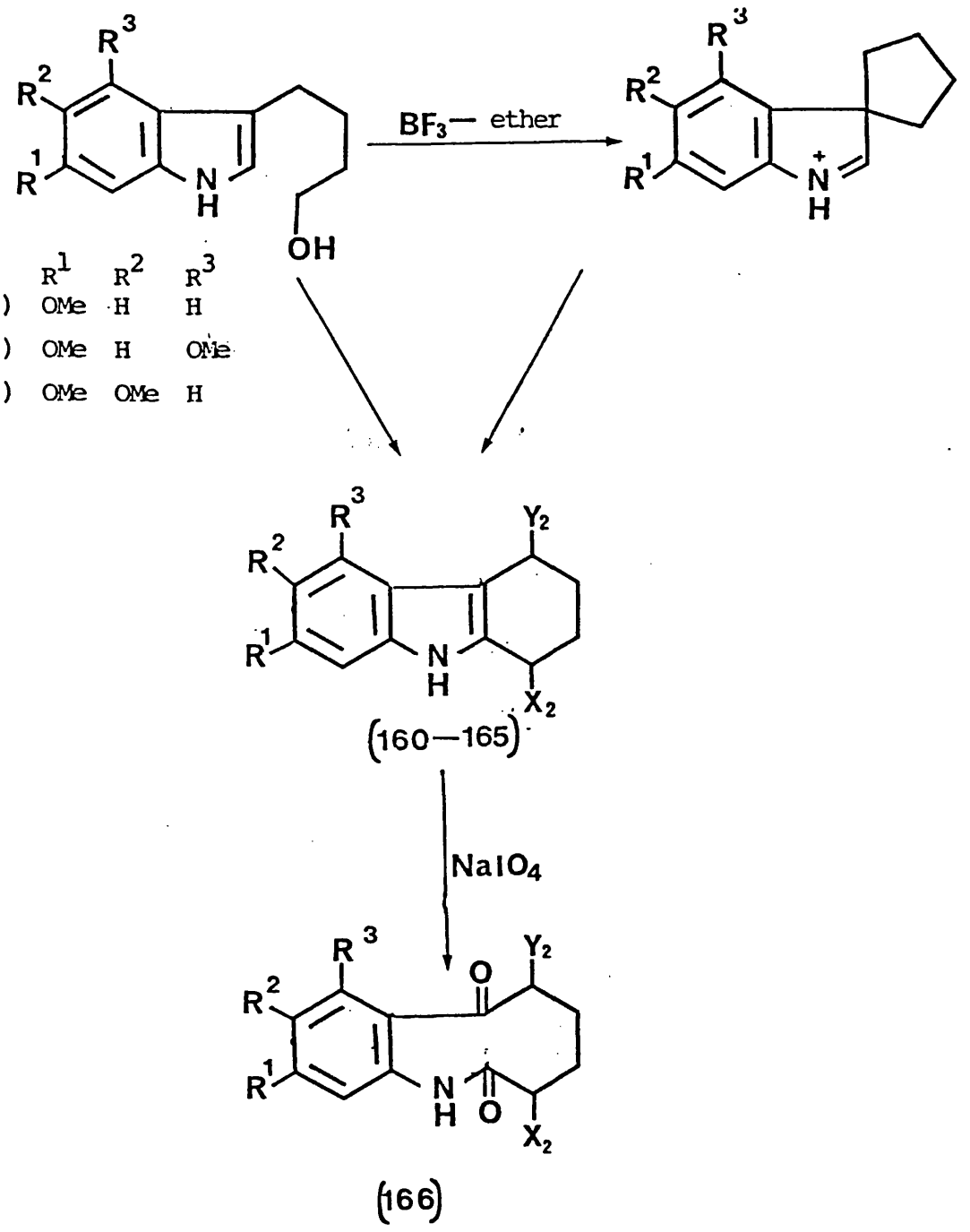
methylene groups was estimated from their resonances in the n.m.r. spectrum (in trifluoroacetic acid).

The assignments were made on the basis of comparisions with the position of the methyl signals in the spectrum of acetanilide and acetophenone.

These results (the n.m.r. studies) of the oxo-amides derived from the 1,1-dideuteriated alcohol showed that the direct attack involved 27% at the 2-position and 73% indirect attack at the 3-position.

Similarly the cyclised products from 4-(4,6-dimethoxyindol-3-yl)-butanol and 4-(5,6-dimethoxyindol-3-yl) butanol were treated with metaperiodiate and analysis of the labelling using the above procedure gave the results shown in Scheme 81.

These results clearly indicate that although the electron donating groups at C-4 and C-6 of indolylbutanols results in an increase in yields of the tetrahydrocarbazoles arising from direct attack at the 2-position, the major pathway is still the spiroindolenine route.



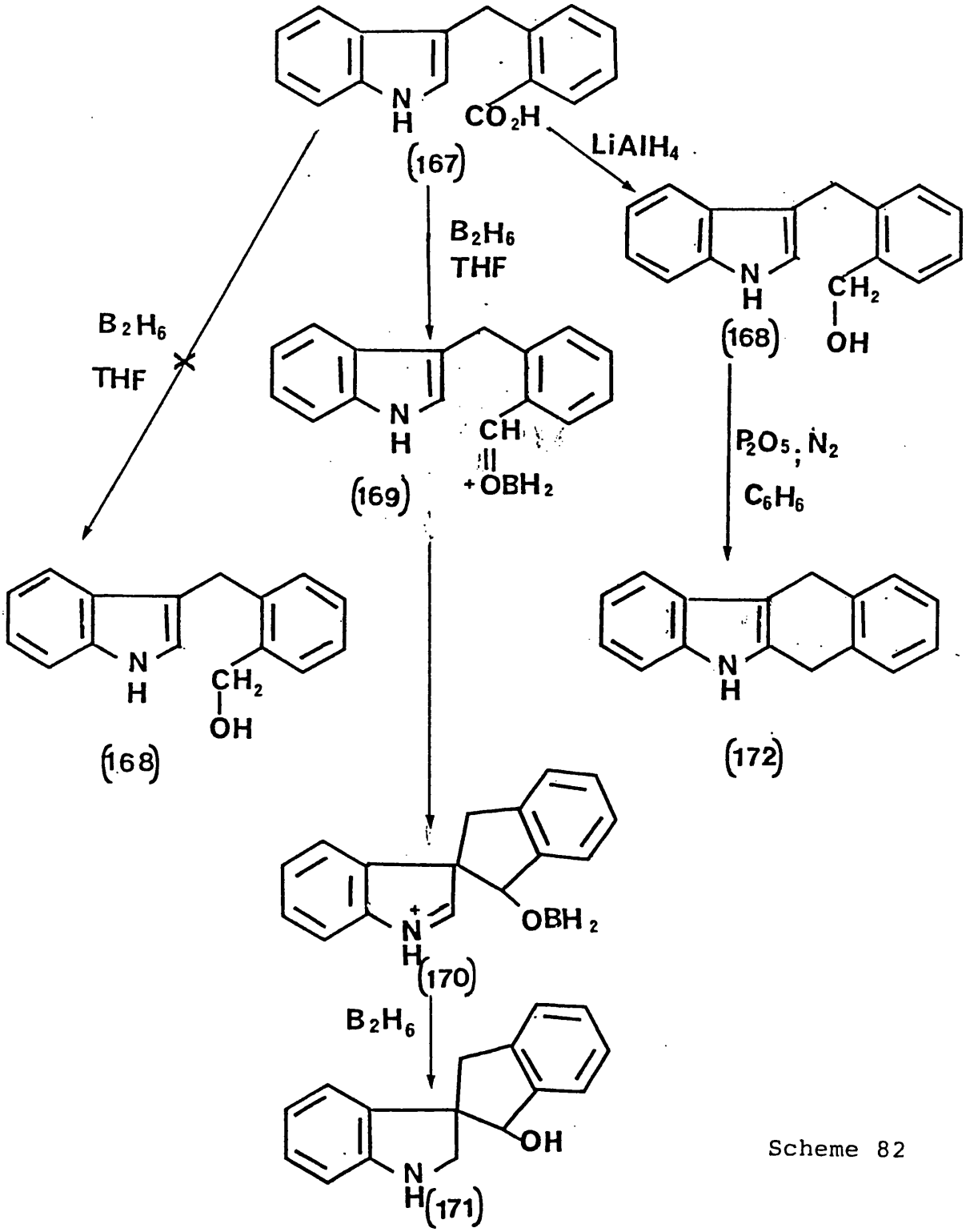
	R^1	R^2	R^3
(152)	OMe	H	H
(158)	OMe	H	OMe
(159)	OMe	OMe	H

Compound	R^1	R^2	R^3	X	Y	Yield(%)
160	OMe	H	H	^{2}H	H	27
161	OMe	H	H	H	^{2}H	73
162	OMe	H	OMe	^{2}H	H	38.5
163	OMe	H	OMe	H	^{2}H	61.5
164	OMe	OMe	H	^{2}H	H	13.5
165	OMe	OMe	H	H	^{2}H	86.5

Scheme 81

Cyclisation of 3-(o-hydroxymethylbenzyl) indole

Strong evidence[125] for the spirocyclic indolenine was seen in the diborane reduction of the carboxybenzylindole (167), the expected alcohol (168) was not formed (Scheme 82); instead, the spiroindoline (171) was isolated. Biswas and Jackson[125] postulated that this presumably was formed through the intermediates (169 and 170).



Scheme 82

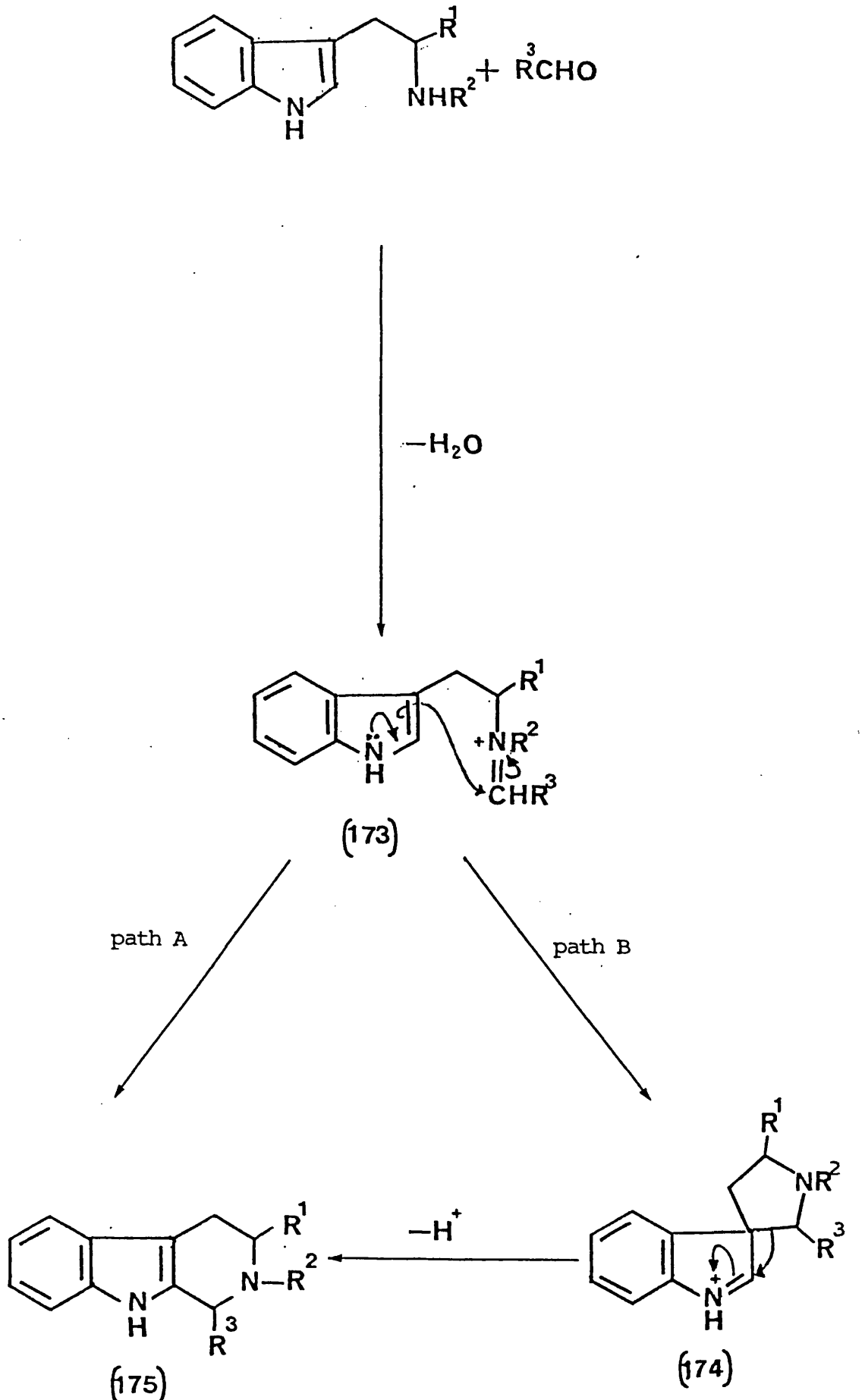
The structure of the spiroindoline was fully characterised by spectroscopic data. However when the same carboxybenzylindole (167) was reduced with lithium aluminium hydride, the alcohol (168) was isolated, which was condensed using phosphorus pentoxide in hot benzene to yield the 1,4-dihydro-2,3-benzcarbazole (172).

Isolation of the spiroindolenine derivative (171) from the reduction (using diborane, Scheme 82) provided strong evidence for the occurrence of spirocyclic intermediate (170), which had been trapped by reduction of the indole-1,2-double bond (170) before rearrangement could take place.

The Pictet-Spengler synthesis of tetrahydro-β-carbolines

The Pictet-Spengler condensation of tryptamines derivatives with aldehydes has been proposed[119,122,132-143] to proceed via two principal mechanistic pathways: the spiroindolenine route (Scheme 83, path B), which is thought to arise by electrophilic attack of the Schiff base (173) at the 3-position of the indole, followed by Wagner-Meerwein type rearrangement to form the product (175); or the simpler pathway which involves the direct attack at the 2-position of the indole (path A).

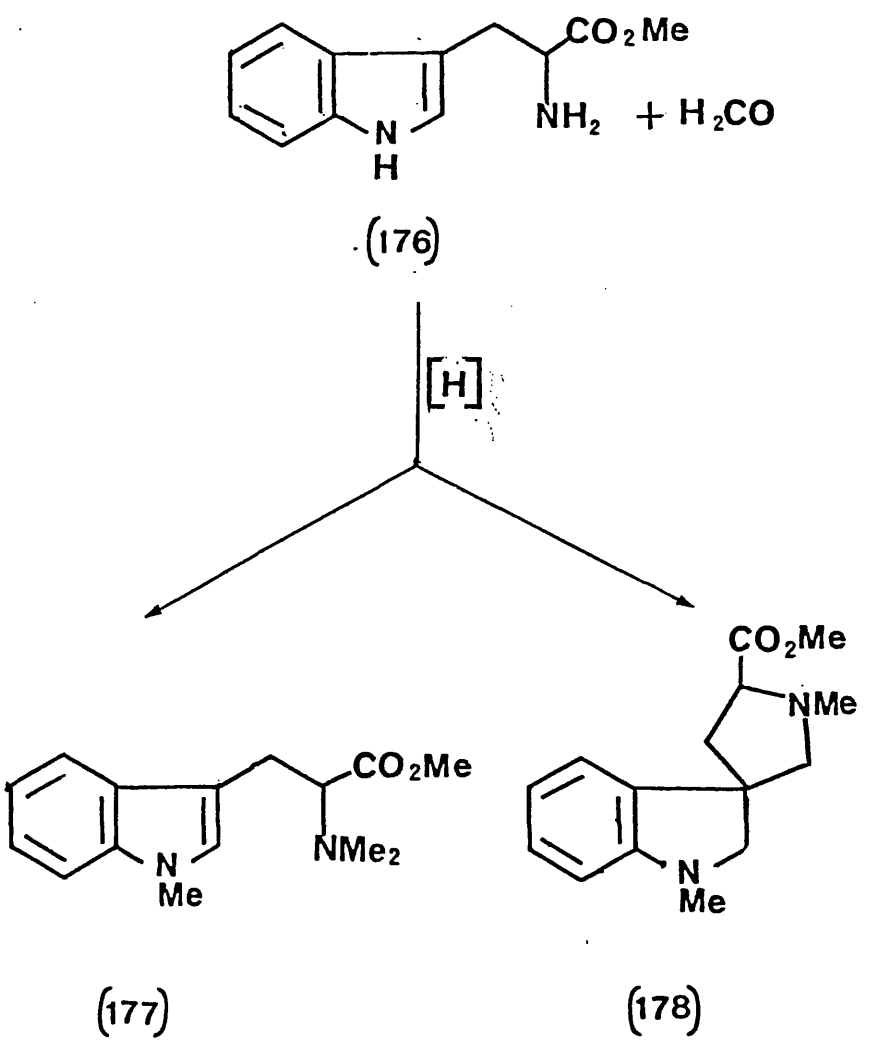
Reports about either of these two mechanisms have appeared in several journals and, in general, strongly favour the spirocyclic-intermediate (174) as the key step in this reaction.


R1
NHR2
+ R3CHO
N
H
−H2O
R1
+NR2
CHR3
N
H
(173)
path A
path B
R1
NR2
R3
N
H
(174)
−H+
R1
N—R2
R3
N
H
(175)

Scheme 83

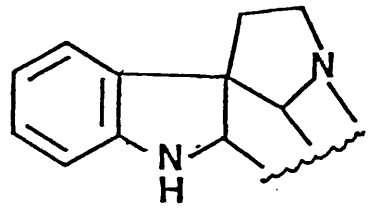
Evidence for the spirocyclic-intermediates in the Pictet-Spengler reaction have been provided by Williams and Unger[132], who have been able to trap the unstable spiroindolenine intermediate.

Thus reaction of tryptophan methyl ester (176, Scheme 84) with excess of dry formaldehyde and hydrogen in the presence of Raney nickel or 5% palladium on charcoal, afforded a mixture of two products, which were separated by chromatography to yield an ester (177, together with the spirocyclic-indoline (178).



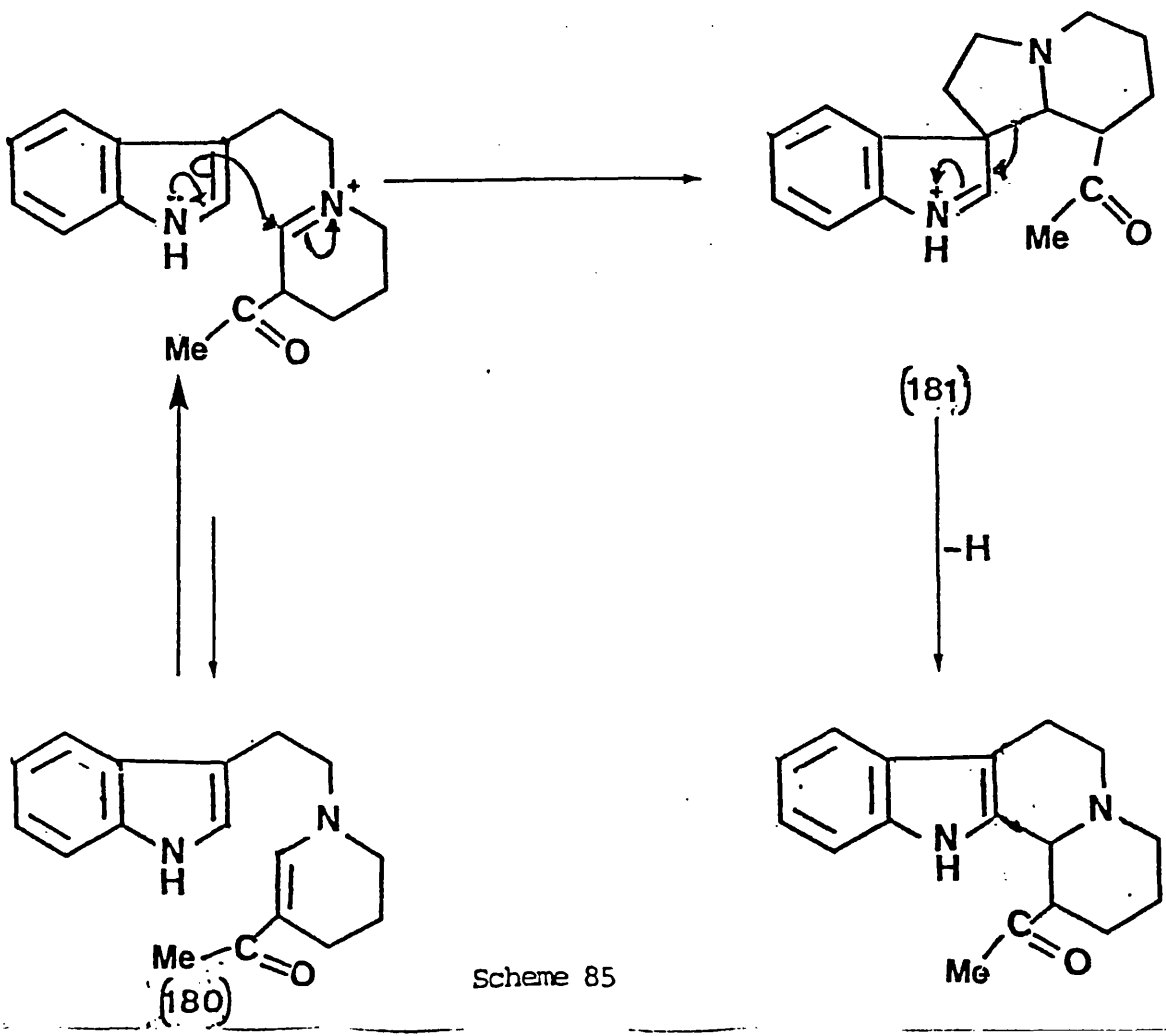
Scheme 84

The powerful evidence that Schiff bases of tryptophan undergo cyclisation by initial attack at C-3 position of the indole ring[135] and its relevance to the biogenesis of indole alkaloids, prompted Wenkert[136] to explore this route to the total synthesis of Aspidosperma alkaloids. These and the strychnos group belong to the β-series of indole alkaloids (179).



(179)

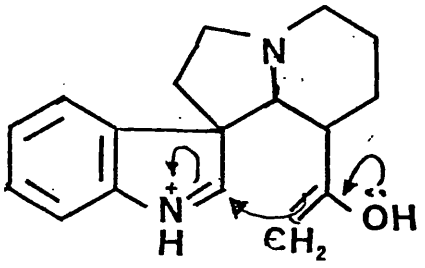
The acid catalysed cyclisation of the 1,4,5,6-tetrahydropyridine (180) was known to be a model for tetrahydrocarboline alkaloids, (Scheme 85)



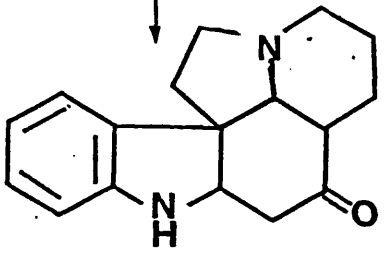
(181)

Scheme 85

and if the reaction occurs via the spiro-indolenine (181), suitable stabilisation of this intermediate could permit the alternative secondary cyclisation to the Aspidosperma nucleus (182) via the enolic form of the ketone (183, Scheme 86a).



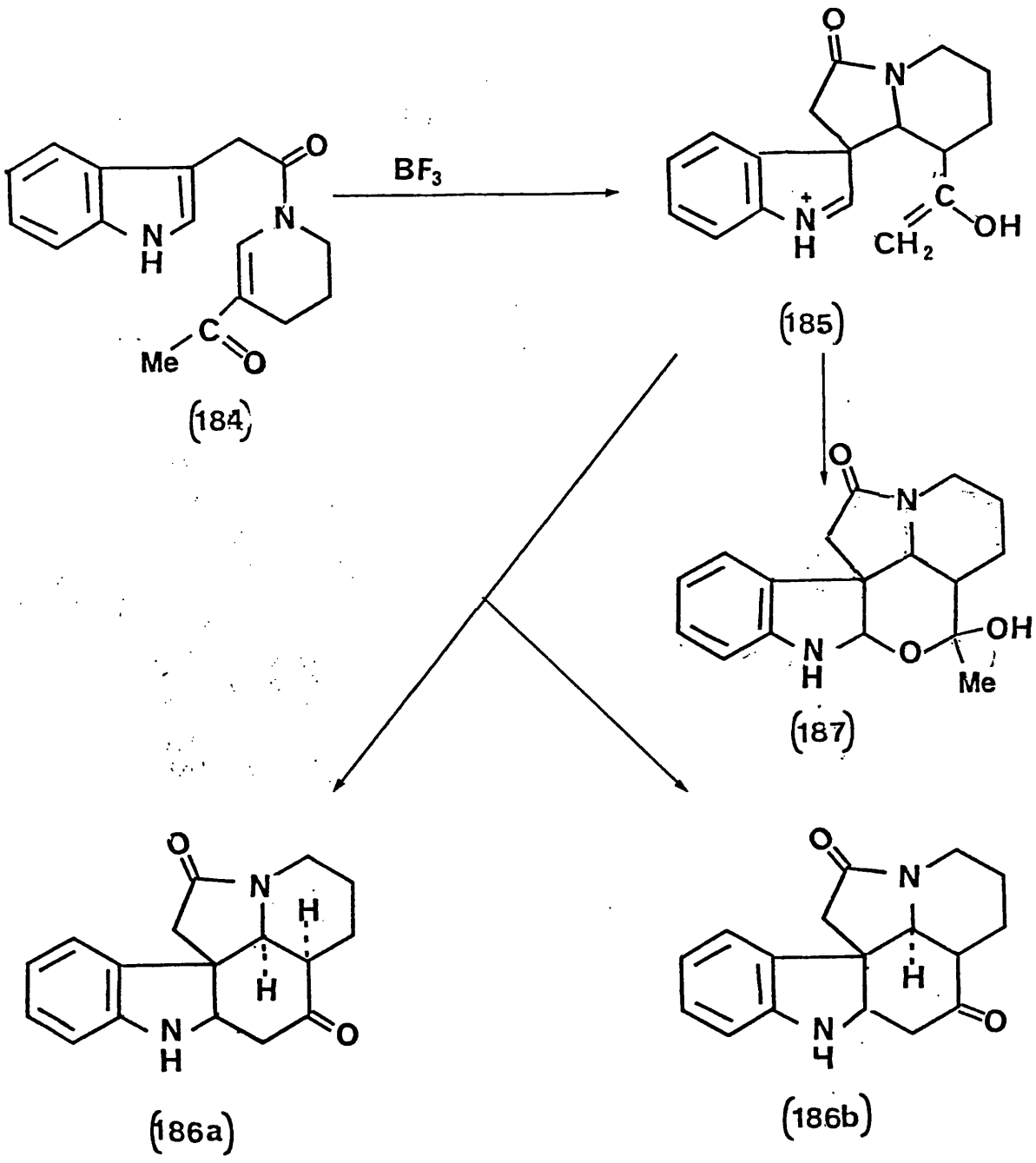
(183)



(182)

Scheme 86a

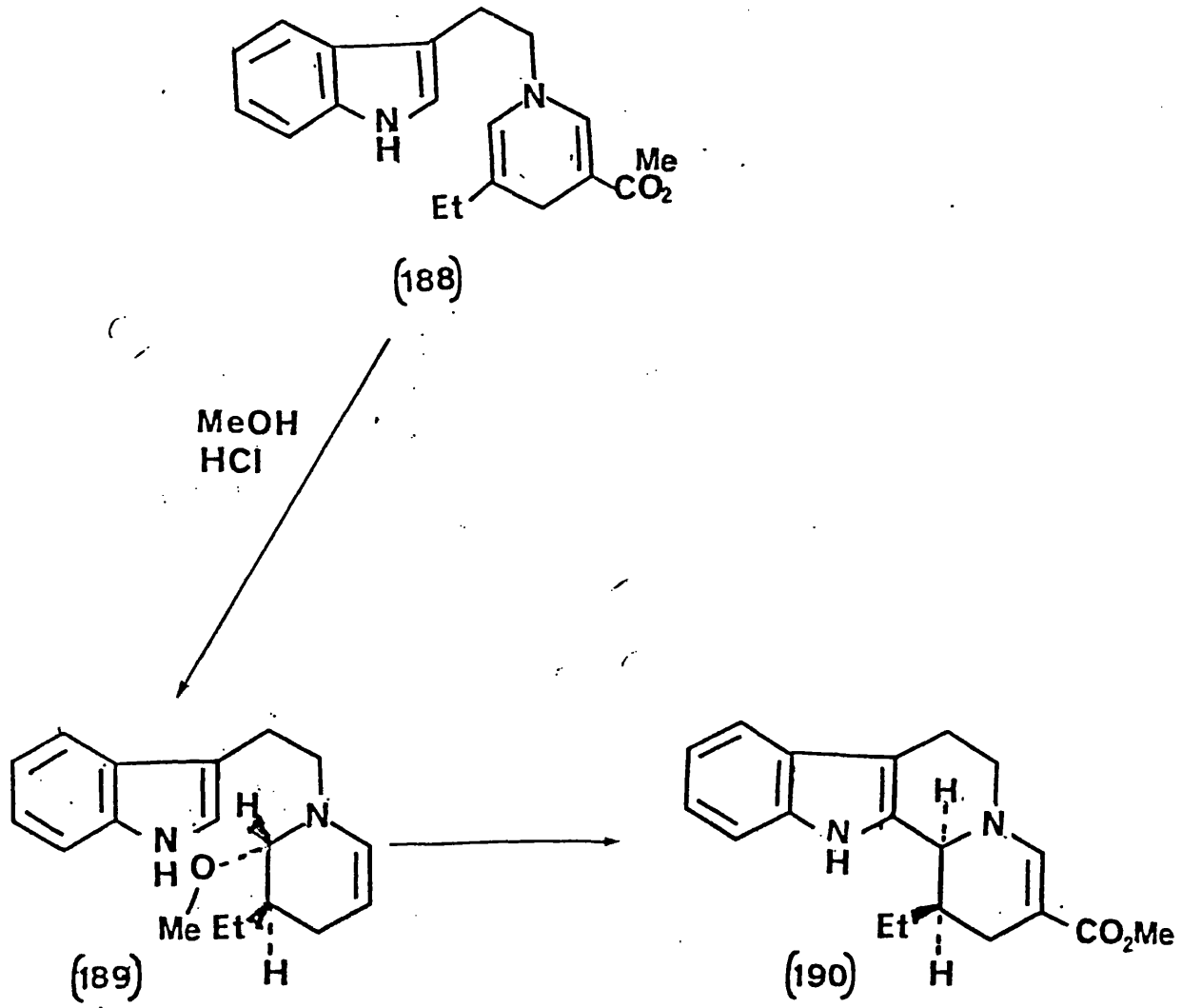
This was achieved by cyclisation of the acyl-tetrahydropyridine (184) which gave a mixture of geometric isomers of the keto-β-lactam (186) via the enol (185) at 85° for 10 min, while at room temperature (12 hr) the hydration product (187) of the intermediate spiro-indolenine was obtained (Scheme 86b).



Scheme 86b

Lounasmaa and Koskinen[137] have reported the acid catalysed cyclisation of the dihydropyridine (188) and on the evidence of ^{1}H and ^{13}C n.m.r. data have assigned the cis configuration to the product (190). These workers argue that this stereospecific cyclisation supports the formation of the intermediate (189) derived from interaction with solvent, which undergoes cyclisation by an Sn2 process, rather than direct involvement of iminium ion which should lead to the trans isomer (Scheme 87).

Although these workers postulate the formation of spiro-indolenine intermediate, Grigg[138] has pointed out that the results could be obtained by direct cyclisation at C-2 of the indole ring.

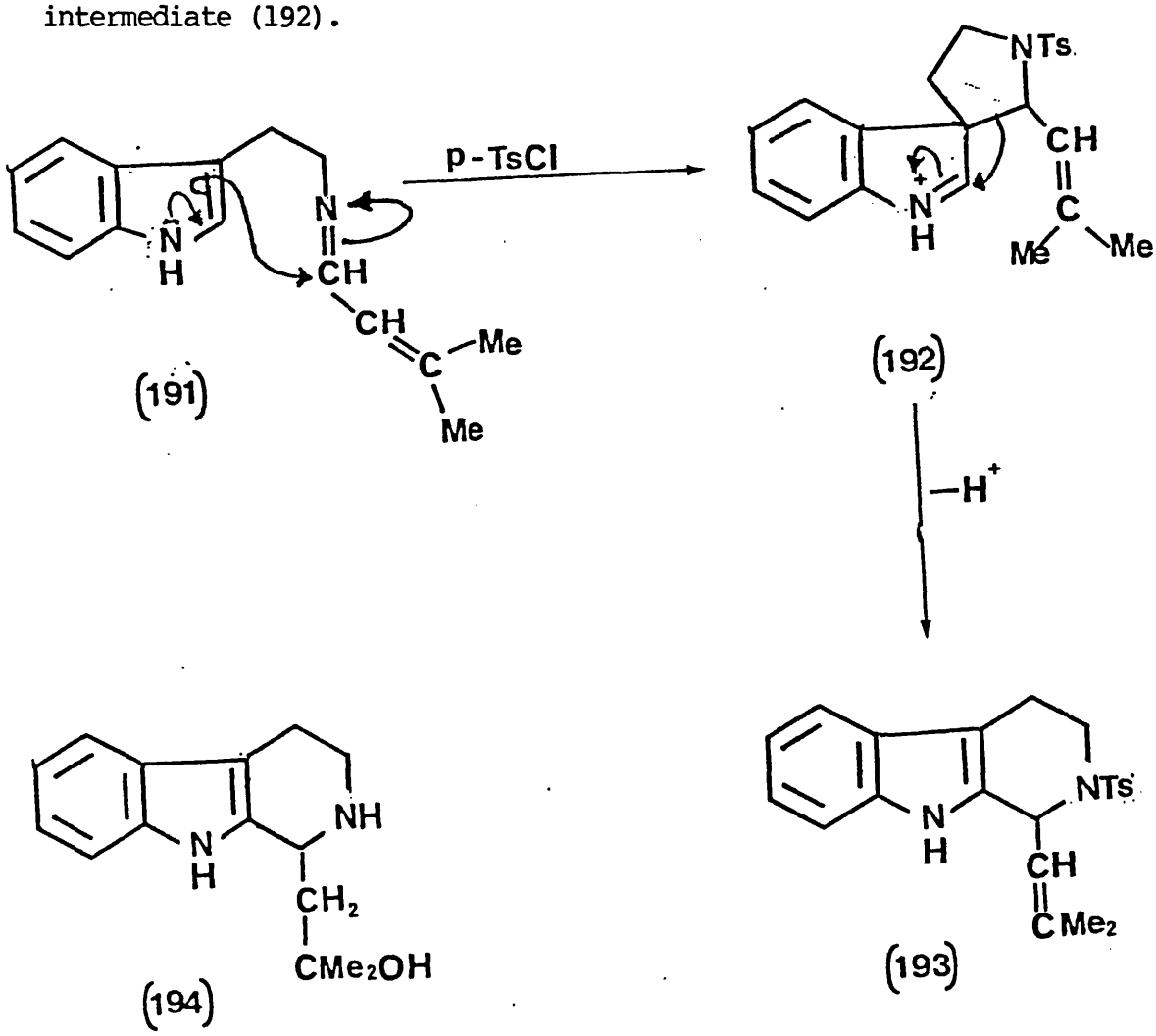


Scheme 87

Harrison[136] has investigated the Pictet-Spengler condensation of the tryptamine derivative with an α,β-unsaturated aldehyde. It was concluded that cyclisation of the resulting Schiff base also occurs via a spirocyclic-intermediate.

Thus condensation of tryptamine with 3-methylbut-2-enal gave the imine (191) which although failing to cyclise under acid conditions, afforded the N-tosyl-tetrahydro-β-carboline (193) upon treatment with p-toluenesulphonyl chloride - pyridine (Scheme 88).

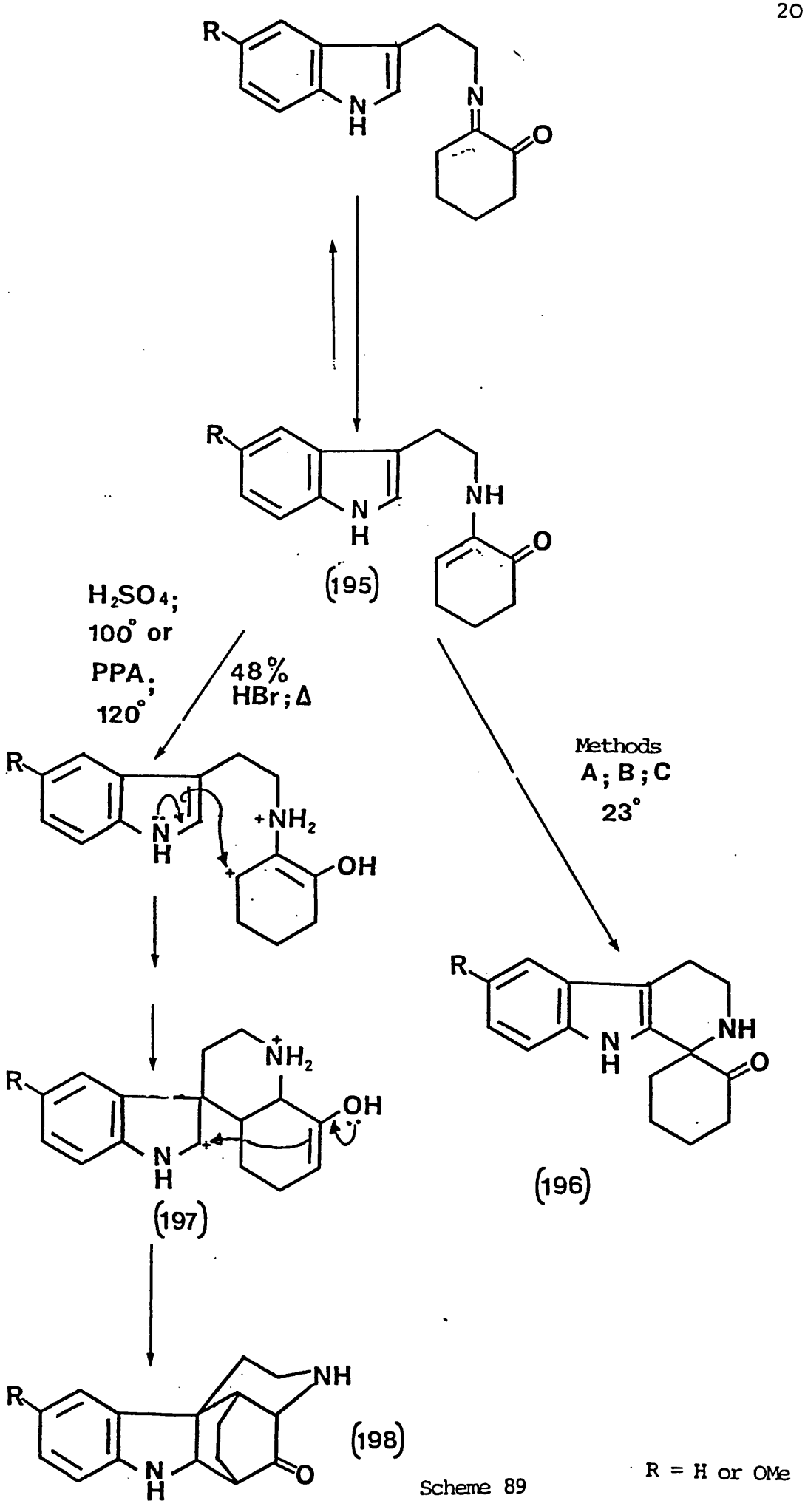
Similarly 3-methylbut-2-enal also condenses with tryptamine in aqueous phophate buffer at pH 6.2 to yield 50% of the tertiary alcohol (194). Again the reaction was postulated to proceed via a spiro-intermediate (192).



Scheme 88

Bobowski[144] has shown that cyclisation of the 2-[[2-(1H-indol-3-yl) ethyl] imino] cyclohexane (195, Scheme 89) with three different acids namely dry hydrogen chloride in chloroform (method A), trifluoroacetic acid (method B), or sulphuric acid in alcohol (method C) gave 2',3',4',9'-tetrahydrospiro[cyclohexane-1,1'-(1H)pyrido[3,4-b]indol]-2-one (196).

Although in a subsequent paper[135] these results were confirmed, it was reported that when the enamine (195, Scheme 89) was exposed to more strenuous conditions, such as concentrated sulphuric acid at 100°, or polyphosphoric acid at 120° or 48% hydrobromic acid heated on a steam bath under nitrogen, the 3,4,9,9a-tetrahydro-1,4-ethano-3,4a-(iminoethano)-4aH-carbazol-2-(1H) one (198) was formed. The formation of this product was again postulated to involve the spirocyclic-intermediate (197).



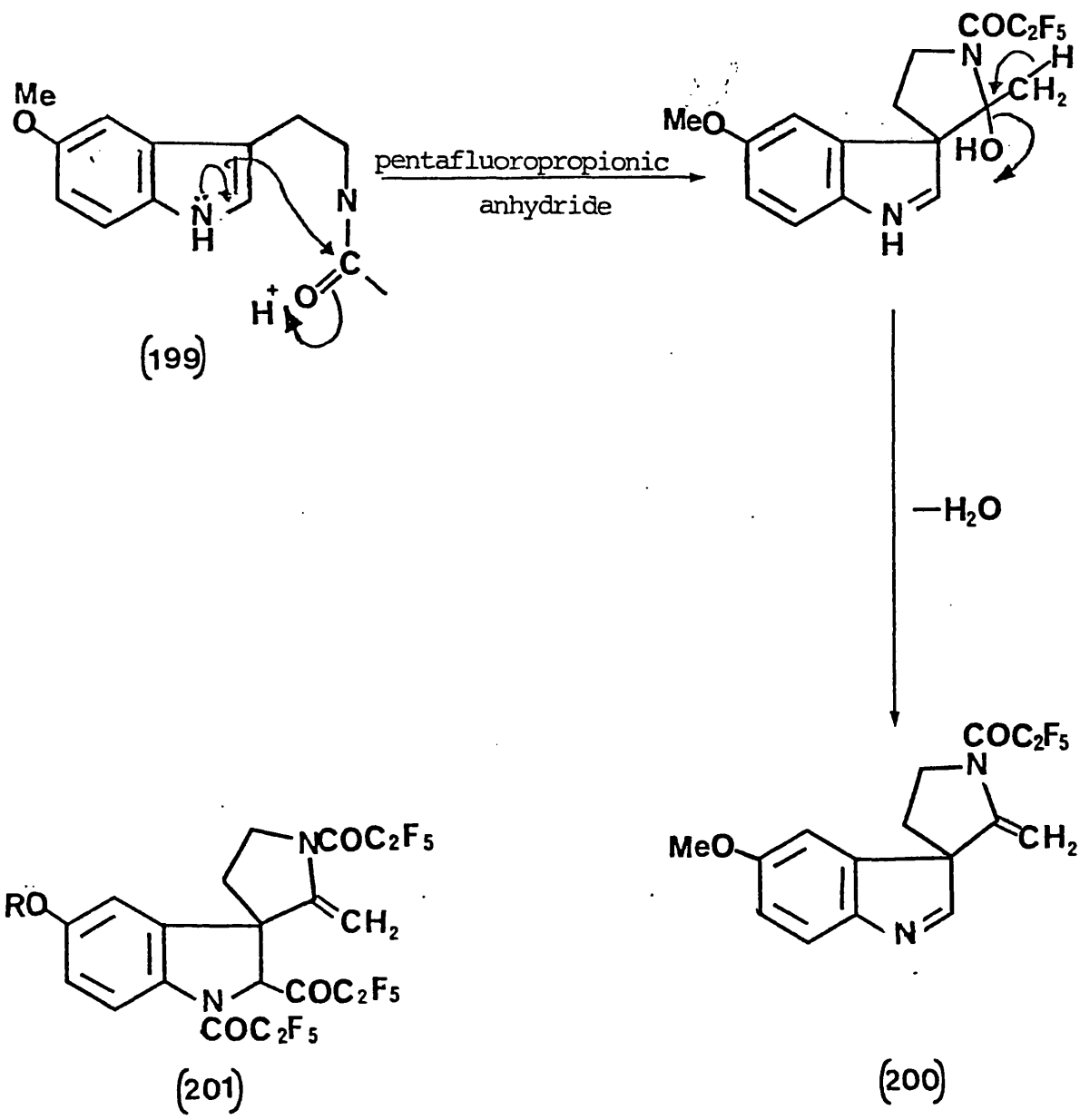
Scheme 89

R = H or OMe

Bischler-Napieralski cyclisation of Acyltryptamines

It is now well established that spirocylic compounds are intermediates in the Bischler-Napieralski synthesis of tetrahydro-β-carbolines from N-acylated tryptamines.

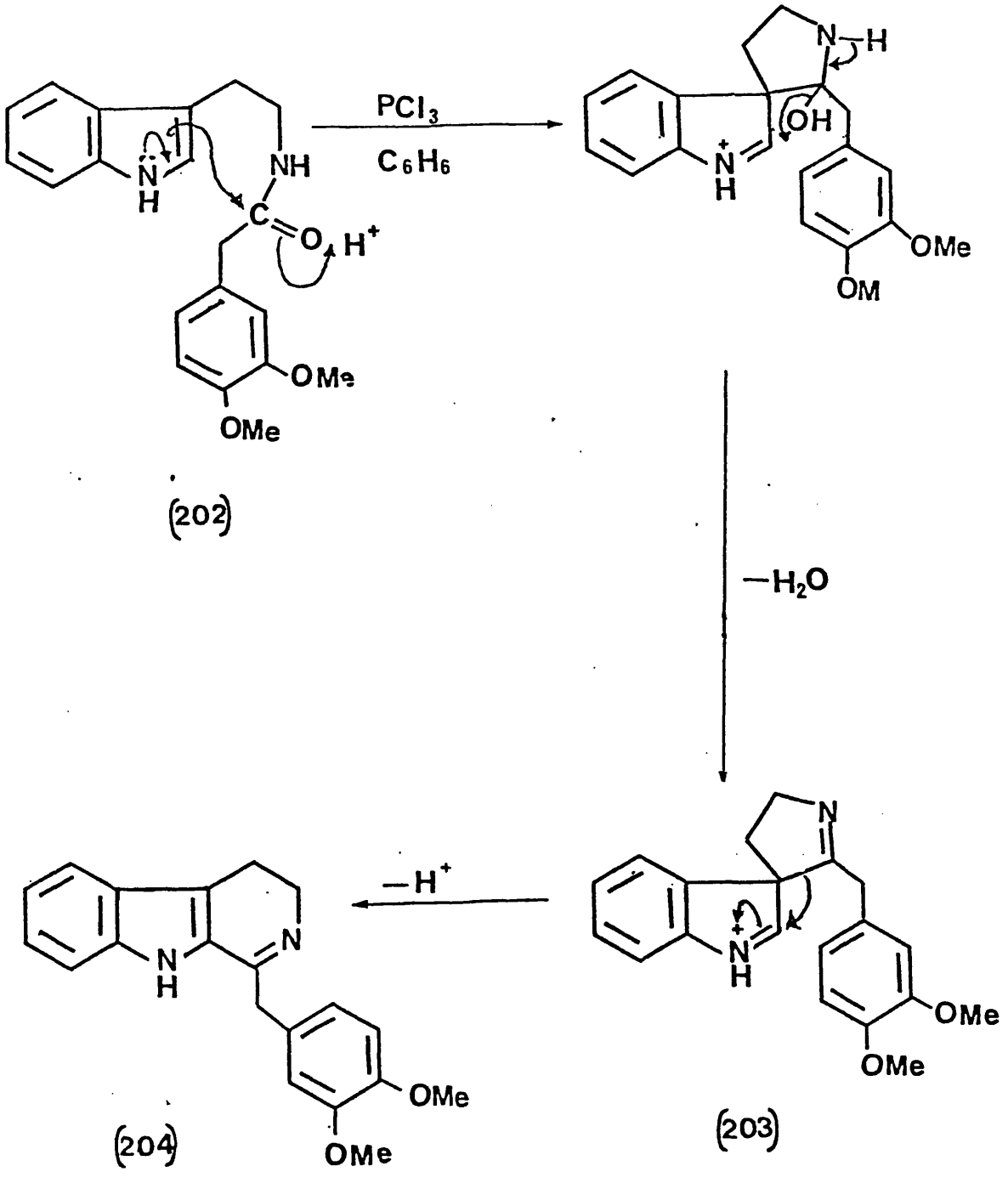
Blau and co-workers[145] have claimed that the structure of the product isolated from heating melatonin (199) in an excess of pentafluoropropionic anhydride was not the expected N-acylated dihydro-β-carboline but the N-acylated indolenine (200, Scheme 90)



Scheme 90

However, Jackson and co-workers[146] in repeating the work of Blau and co-workers[145] and by providing n.m.r. and microanalytical support disputed the above results. Cyclisation of N-acetyltryptamine with pentafluoropropionic anhydride gave the spiro-indoline (201, R=H).

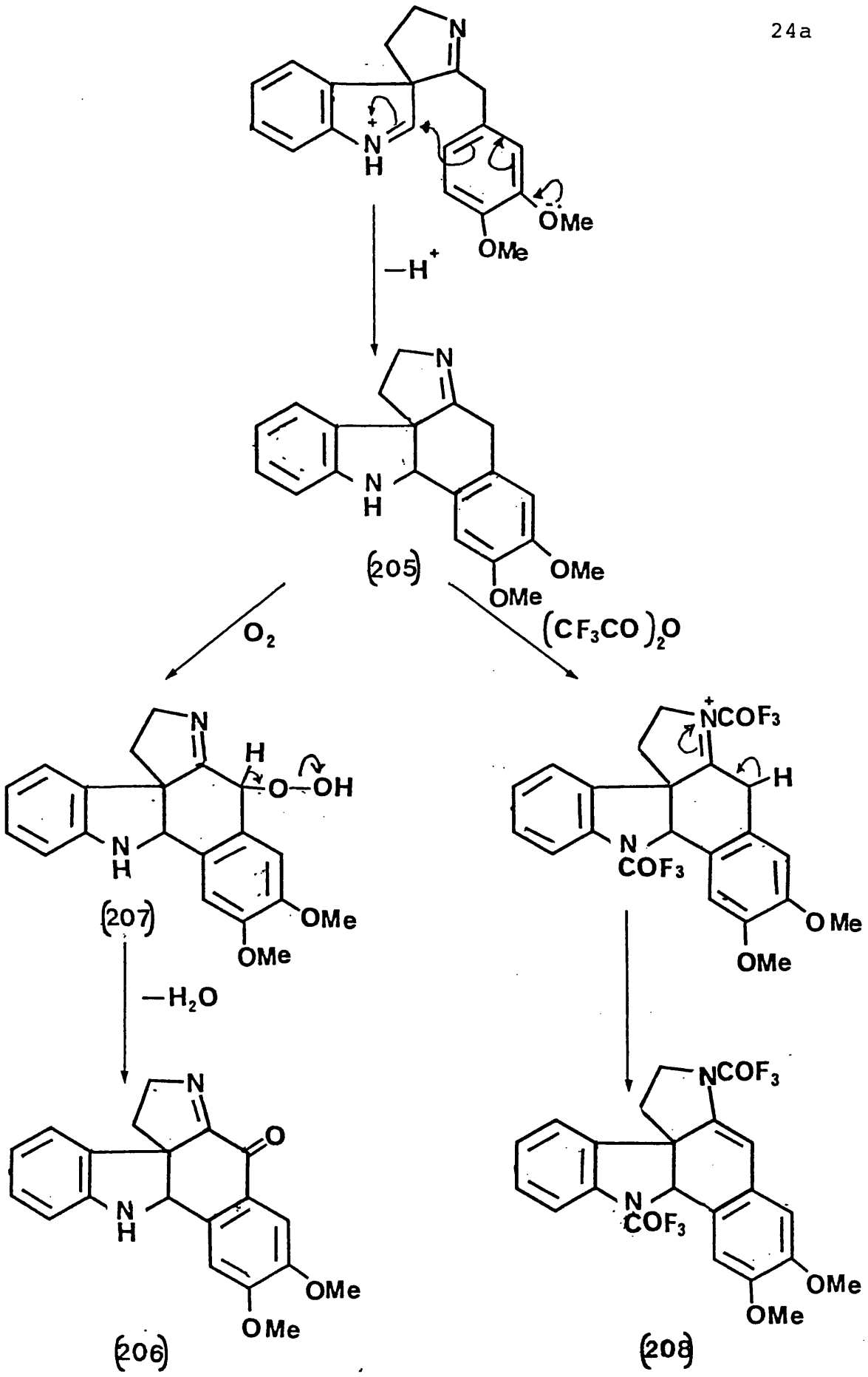
Onda and Kawanishi[147] have reported that phosphorus trichloride-catalysed cyclisation of N-(3,4-dimethoxyphenylacetyl)tryptamine (202, Scheme 91) in boiling benzene afforded the dihydro-β-carboline (204).



Scheme 91

Recently Biswas and Jackson[148] have suggested that the above cyclisation may have proceeded via the spirocyclic indolenine (203). However, when the above work was repeated by these later workers, it was reported that the product isolated was the spirocyclic indoline (206, Scheme 92) in 46% yield. A small amount of hydroperoxide (207) was also isolated. Similar results were obtained using phosphoryl chloride as a cyclising reagent. The authors concluded that the overall sequence of reactions involved in the formation of the spirocyclic indoline (206) presumably follows the route shown in Scheme 91 as far as (205) but autooxidation of this species by molecular oxygen then affords the hydroperoxide (207), which subsequently breaks down by loss of water.

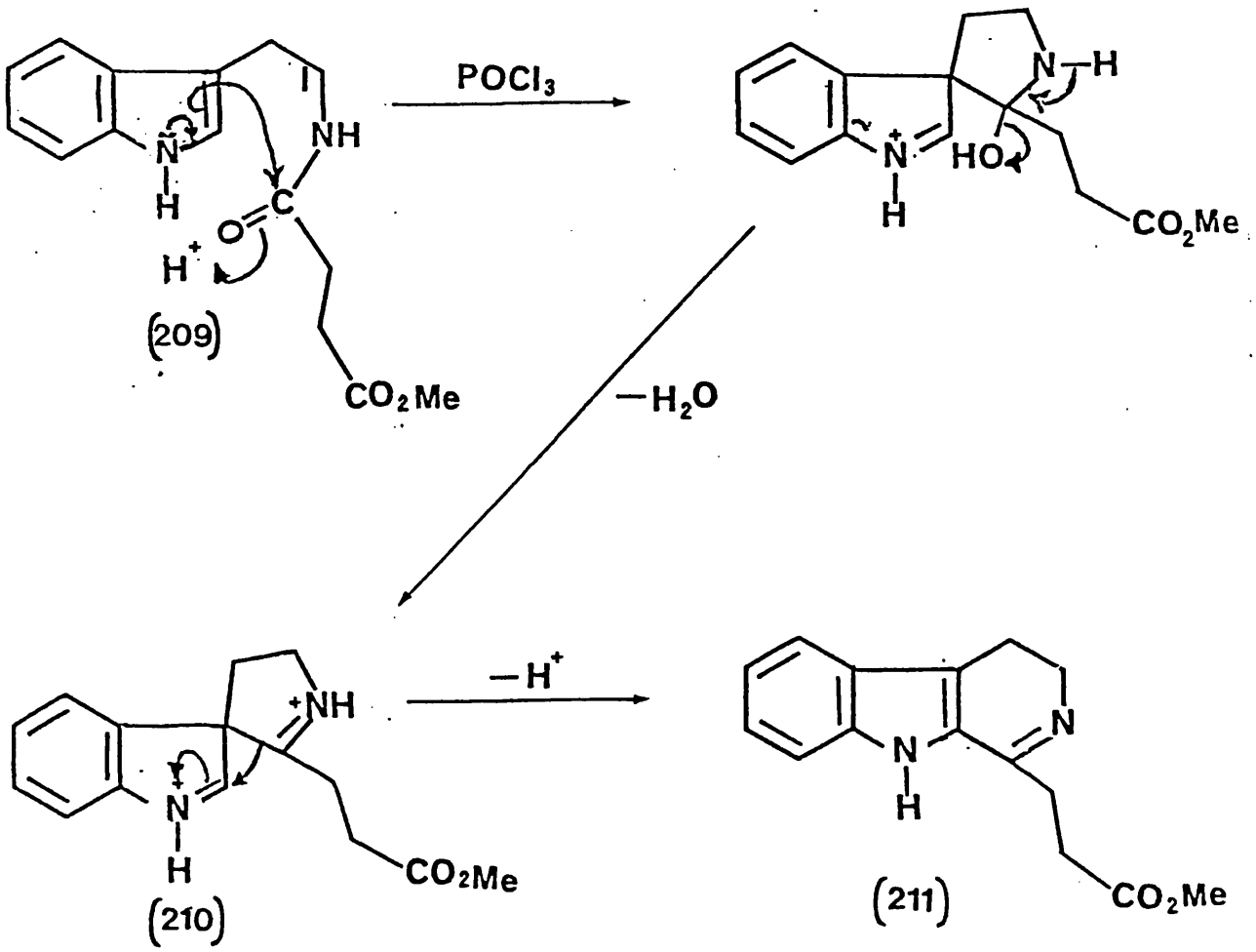
The above reaction when performed using trifluoroacetic anhydride in benzene solution for 3 hours at 0°C, followed by 1 hour at 20° gave the bis-trifluoroacetyl spirocyclic indoline (208, Scheme 92). Biswas and Jackson[148] have suggested that the product (208) could have formed via the spirocyclic-indolenine (203) and the indolenine (205). The structures of the products were elucidated by elemental analyses and by spectroscopic data.



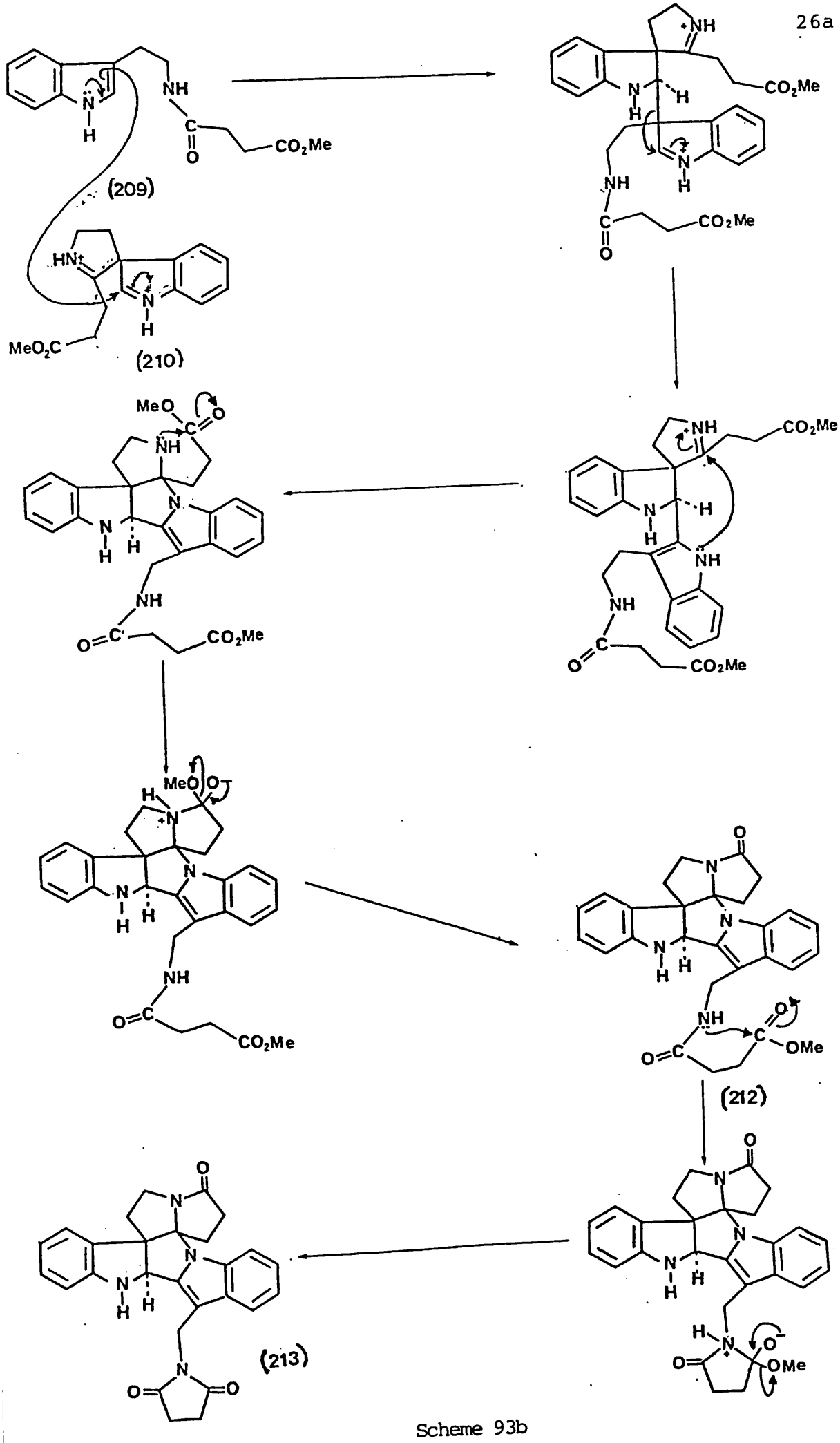
Scheme 92

More recently Frost and co-workers[149] have shown that when the tryptamine derivative (209, Scheme 93a) was treated in acetonitrile with a 10% excess of phosphoryl chloride for one hour at 60°C, it afforded the dihydro-β-carboline (211) in low yield (15%). The major products isolated in pure form by column chromatography were the two fused heptacyclic products (212 and 213) in 28.5 and 25.2% yield respectively (Scheme 93b).

The formation of these products was postulated[149] to have occurred via the spirocycic-intermediate (210), and hence add to exisiting evidence that Bischler-Napieralski cyclisation of the N-acyltryptamines involves initial attack at the indole 3-position.



Scheme 93a



Scheme 93b

Cyclisation of Benzylaminoacetonitriles

Mackay and Waigh[150] have reported the occurrence of spiro-intermediate (215) in cyclisation of skatylaminoacetonitriles (215) using polyphosphoric acid at 80° or sulphuric acid at 0° as a cyclising agents.

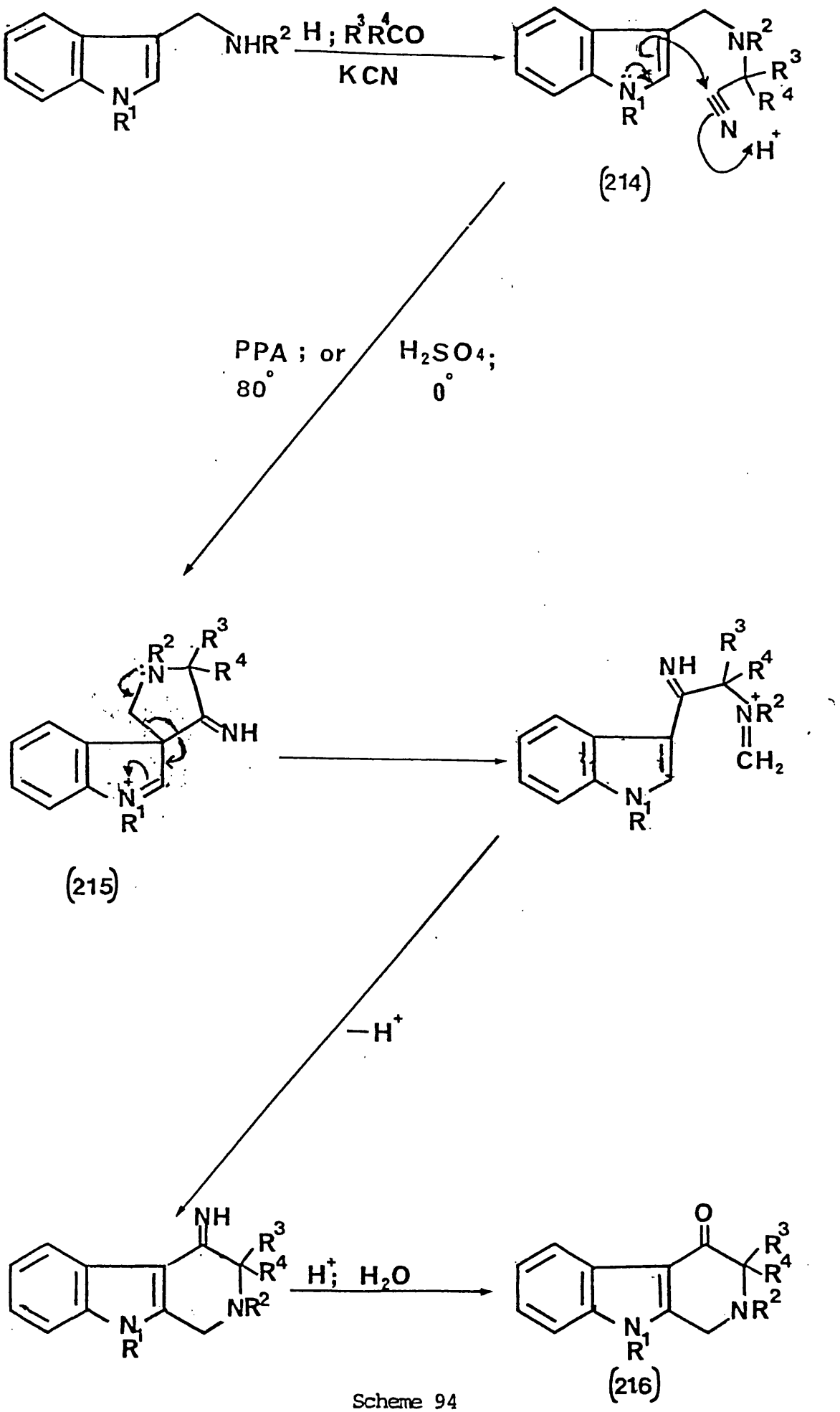
The products, 1,2-dihydro-β-carobolin-4(3H)-ones (216) were obtianed in good yield.

It is interesting to note that cyclisations performed using sulphuric acid as cyclising agent under the conditions used to rearrange benzylaminonitriles resulted in polymerisation and/or sulphonation and that no identifiable products were isolated.

However using the same cyclising agent at lower temperature (0° for 15 minutes) have been shown to give good yields of 1,2-dihydro-β-carbolin-4(3H)-ones (Scheme 94). All the products were characterised by the spectroscopic data and microanalyses.

To establish whether the carbonyl group was attached at C-2 or C-3 of the indole, comparison with directly analogous oxocarbazoles was made. The techniques that were used included infra-red, ^{1}H n.m.r. and U.V. spectroscopy. Thus the carbonyl stretching for 3-acyl indoles is less than 1630 cm^{-1}, whereas for 2-acylindoles it is 30-50 cm^{-1} higher. Similarly the proton n.m.r spectrum of the 3-acyl indoles shows the downfield shift in the benzene-ring proton near to the carbonyl group, whereas in 2-acyl indoles there is no such proton.

The U.V. spectrum of the product showed three bands of similar wavelengths and intensity to the 4-oxocarbazoles, thus confirming that carbonyl group was attached at C-3 of the indole.


NHR2
H ; R3R4CO
KCN
NR2
R3
R4
N
H+
(214)
PPA ; or
80°
H2SO4;
0°
R2
R3
R4
NH
(215)
NH
R3
R4
NR2
CH2
−H+
H+; H2O
O
(216)

Scheme 94

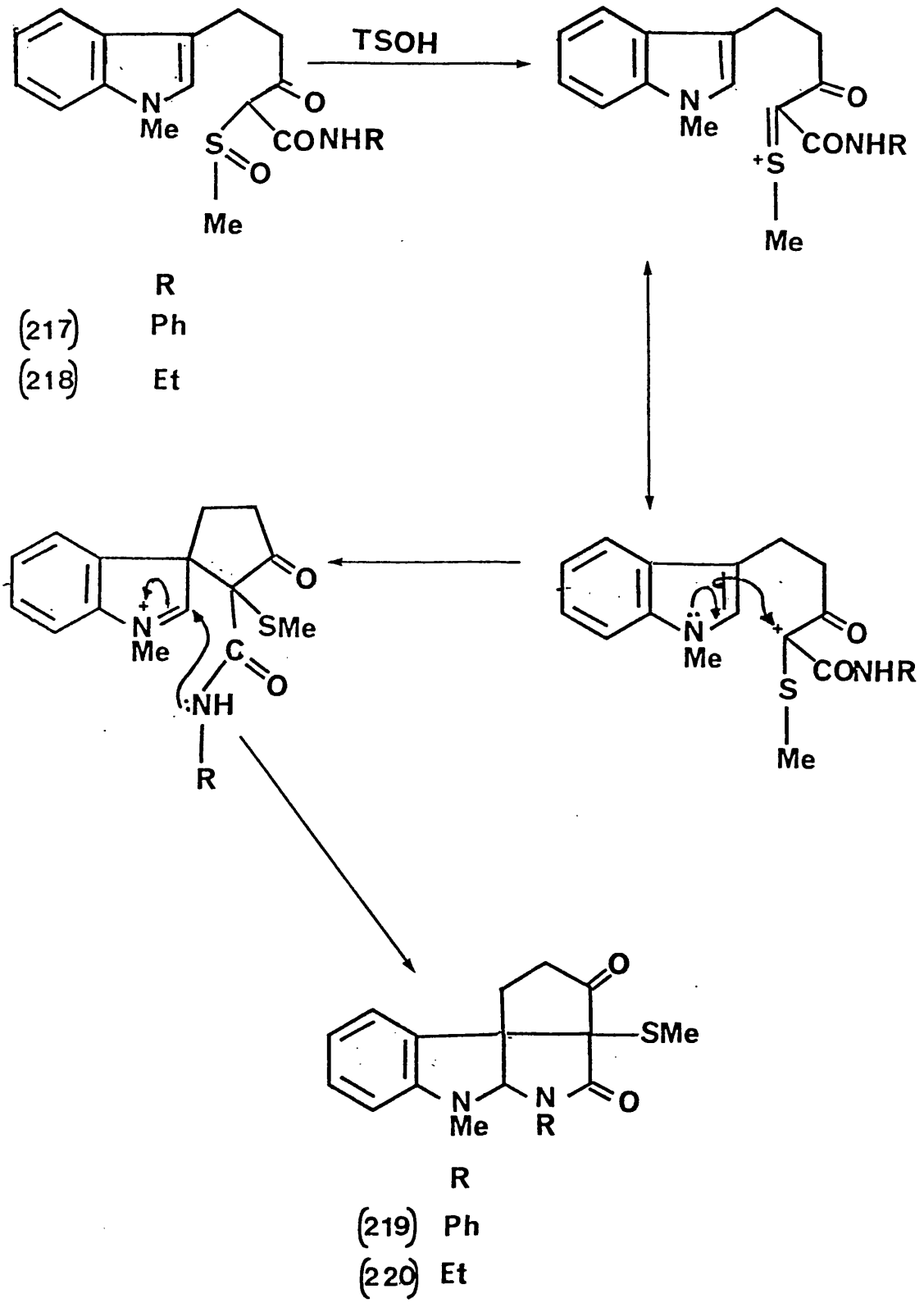
Cyclisation of β-keto sulphoxides

Further evidence for the occurrence of a spiro-intermediate in organic reactions is seen in the cyclisation of β-keto sulphoxides,[151] which upon treatment with trichloroacetic acid or trifluoroacetic acid gave tetrahydrocarbazoles.

However, cyclisation has been reported[151] to proceed more smoothly when toluenesulphonic acid in tetrahydrofuran was employed. Thus treatment of the β-ketosulphoxide (217, R=C_6H_5) with toluenesulphonic acid in acetonitrile, (217, R=C_6CH_5) interestingly gave mainly a tetracyclic compound (219, R=C_6H_5), as well as the expected product (221, R=C_6H_5) in 45% and 30% yield respectively. Similarly, (218, R=Et) gave (220 and 222) in 41 and 35% yield respectively (Scheme 95).

However, cyclisation performed under milder conditions, that is, when exposed to toluenesulphonic acid at 50° in dioxane the β-keto sulphoxide (218) gave the compounds (220 and 223) in 40 and 44% yield respectively.

The isolation of the tetracyclic products (219 and 220) has provided additional evidence for the presence of the spirocyclic indolenine in the electrophilic substitution of 3-substituted indoles by direct trapping.



R

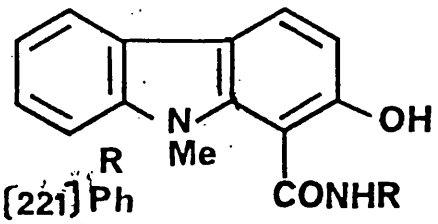
(217) Ph

(218) Et

R

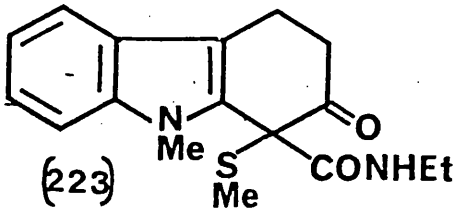
(219) Ph

(220) Et



(221) Ph

(222) Et



(223)

Scheme 95

Cyclisation of 3-(2-pyrrolyl)propionic acids

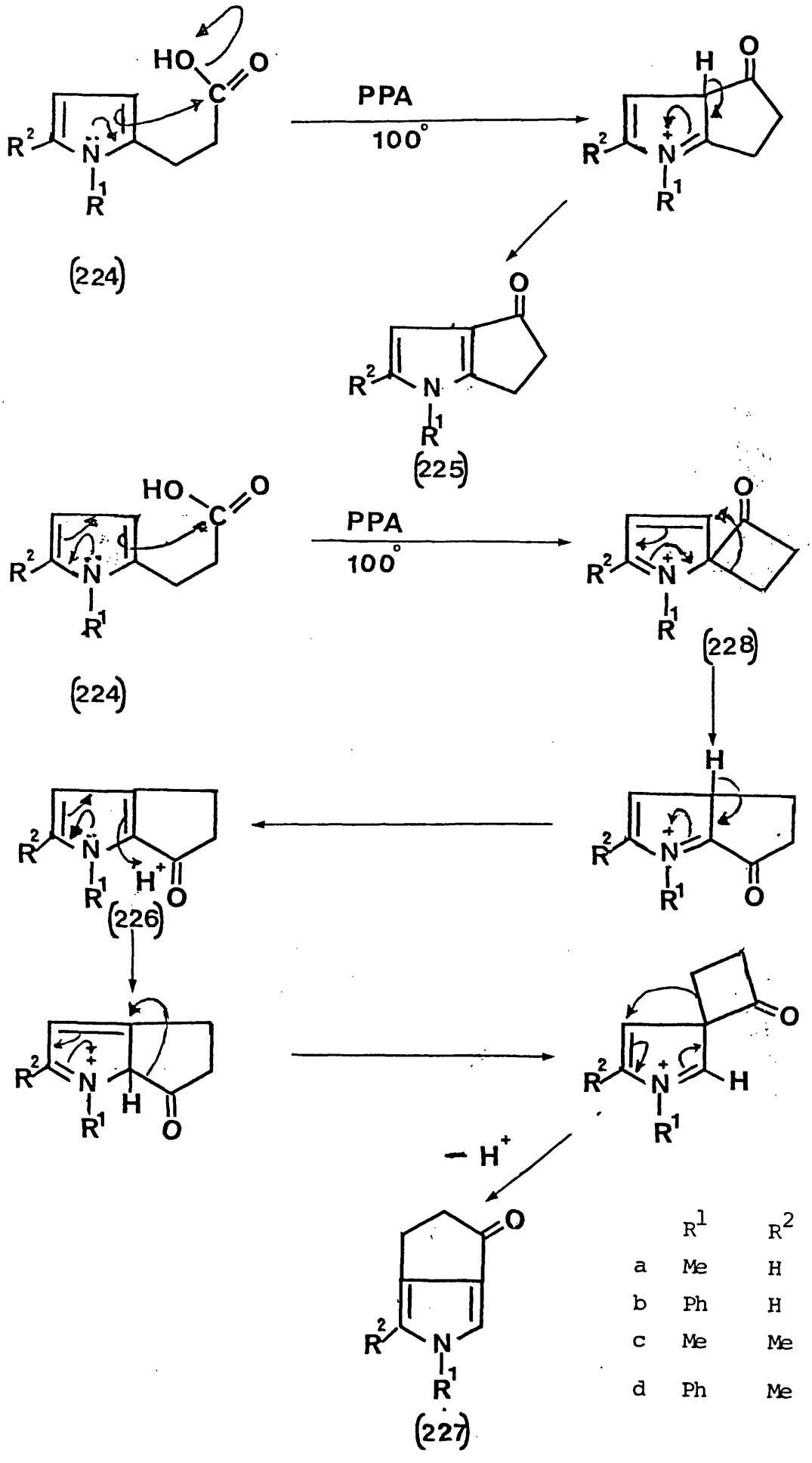
Palmer and co-workers[152] have reported that cyclisation of 3-(2-pyrrolyl)propionic acids (224, Scheme 96) using polyphosphoric acid (PPA) at 100°C gave mixtures of 4H-cyclopenta[b]pyrrol-4-ones (225), the corresponding 6-ones (226) by a single rearrangement and the cyclopenta[c]-pyrrol-4-ones (227) by a double rearrangement, which were separated by column chromatography. The proportions of each product depended upon the substituents.

The formation of compounds (226 and 227) has been postulated to have occurred via the spirocyclic intermediate (228, Scheme 96).

Thus cyclisation of (244a) gave the major product 4H-cyclopental [b]- pyrrol-6-one (226a) and the corresponding minor product 4-one (225a) in 64 and 36% yield respectively.

However, the 1-phenyl compound (224b) gave a mixture of three isomeric ketones, which were separated by alumina chromatography to give the 6-one (226b, 47%), the 4-one (225b, 30%) and the 4H-cyclopenta[c]-pyrrol-4-one (227b, 8%).

The authors claimed that, when the pair of 5-methyl acids (224 c,d) were treated with polyphosphoric acid, only single products were obtained, and in each case these were the 6H-cyclopenta[b]-pyrrol-6-ones (226 c,d), hence postulating that rearrangement (via a spirocyclic intermediate) had occurred exclusively (Scheme 96).



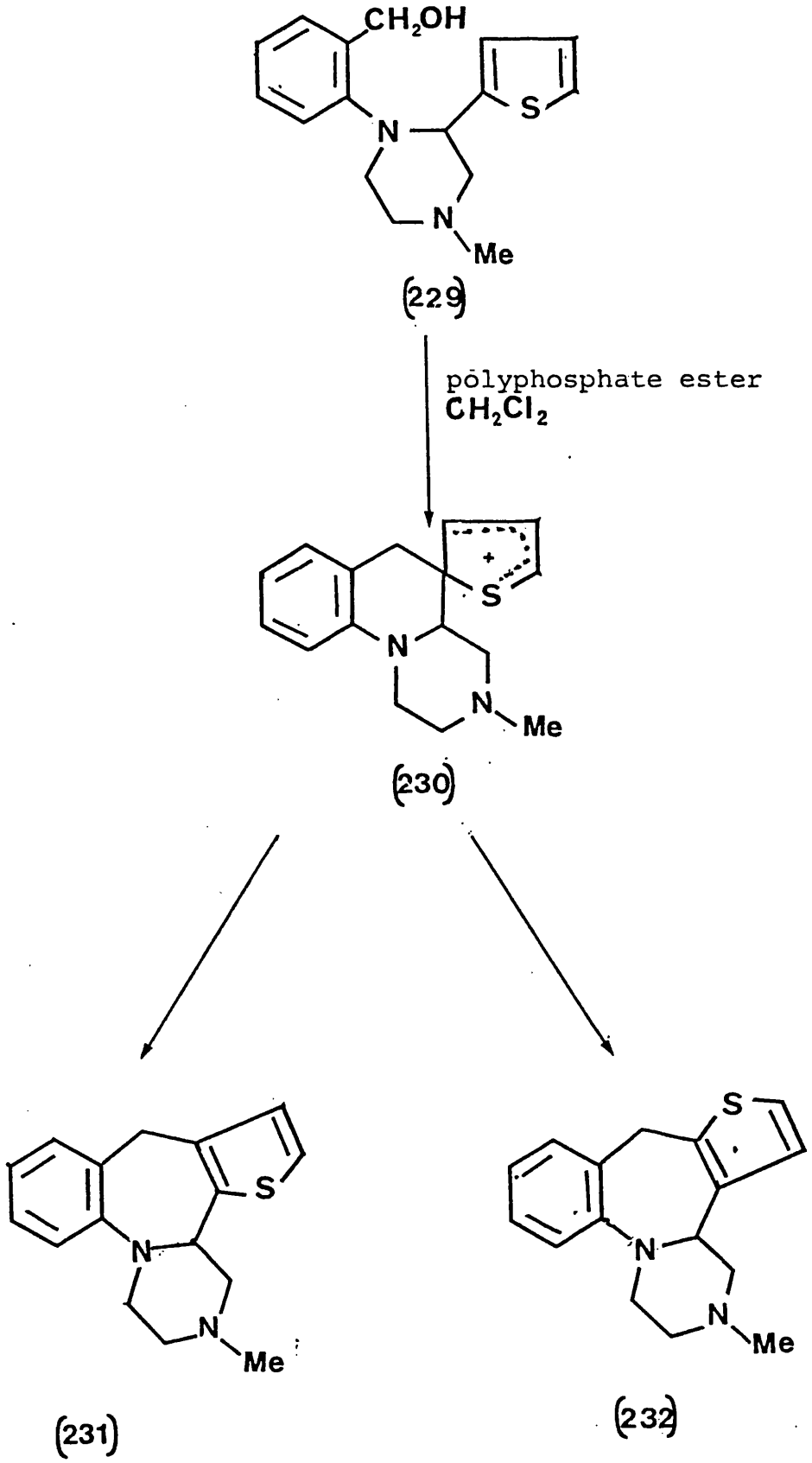
	R^1	R^2
a	Me	H
b	Ph	H
c	Me	Me
d	Ph	Me

Scheme 96

Cyclisation of 1-[2-(hydroxymethyl]-4-methyl-2-(2-thienyl)piperazine

More recently Whatthey and co-workers[153] have reported further examples of spirocyclic intermediates in heterocyclic chemistry involving the synthesis of thiophene-containing analogues of mianserin.

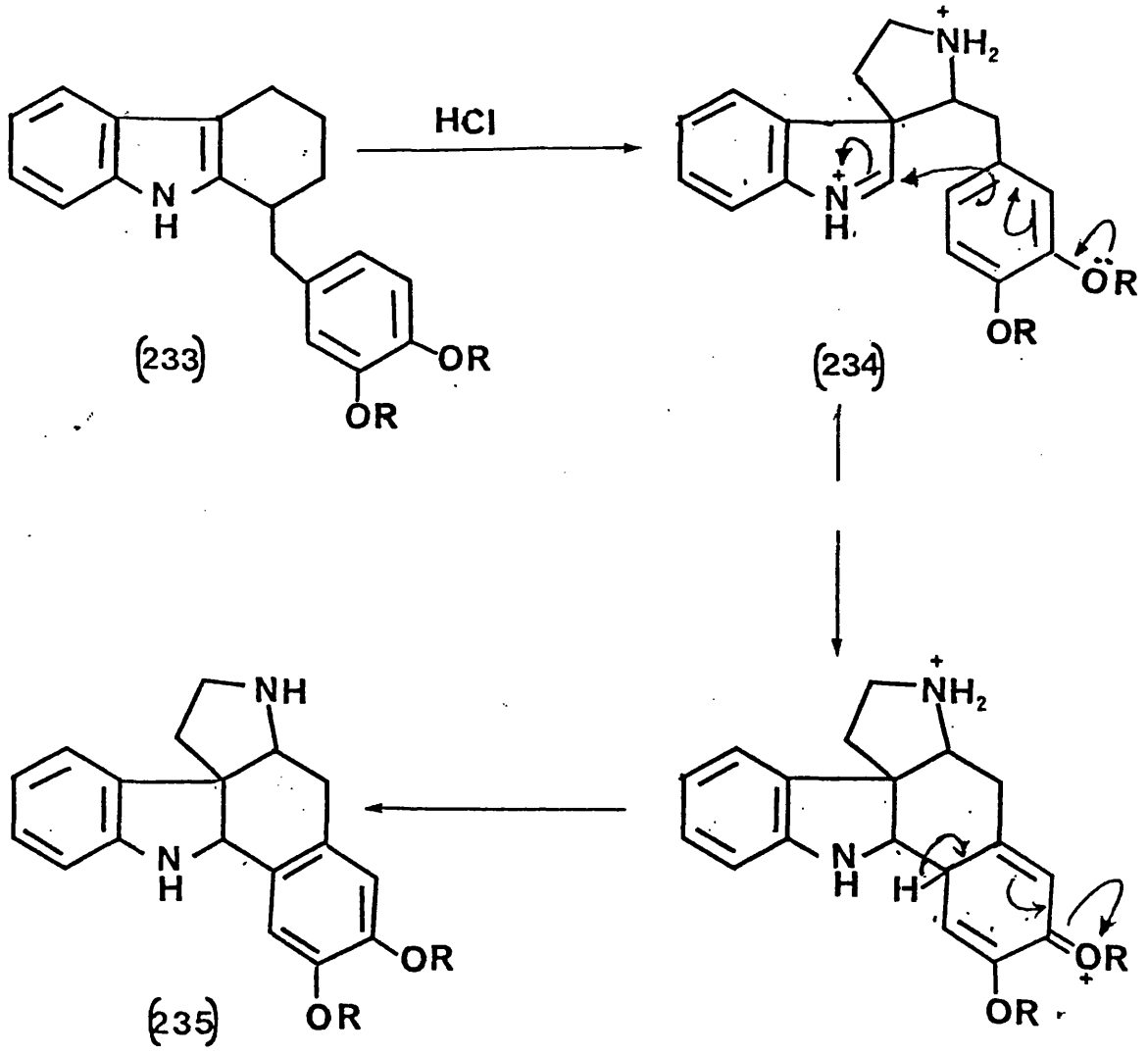
Thus cyclisation of 1-[2-(hydroxymethyl)phenyl]-4-methyl-2-(2-thienyl)piperazine (229) with polyphosphate ester in refluxing dichloromethane have been shown to yield the benzazepines (231 and 232) in a ratio of 5:1. It was suggested that these products were formed via a spiro-intermediate (230) and that the process involves formation of a six-membered ring with substitution onto the more reactive α-position of the thiophene ring, followed by collapse of the spiro-intermediate to either 1,2,3,4,10,13b-hexahydro-2-methylpiperazino[1,2-a]thieno[2,3-c][1]benzazepine (231), or the corresponding [3,2-c]isomer (232, Scheme 97).


CH2OH
S
N
N
Me
(229)
polyphosphate ester
CH2Cl2
S
N
N
Me
(230)
S
N
N
Me
(231)
S
N
N
Me
(232)

Scheme 97

Rearrangement of the tetrahydrocabolines

Rearrangement of the tetrahydrocarbolines (233) in boiling concentrated hydrochloric acid to the spirocyclic indolines (235) has been postulated[123,124] to occur via the the spirocyclic indolenines (234, Scheme 98).



Scheme 98

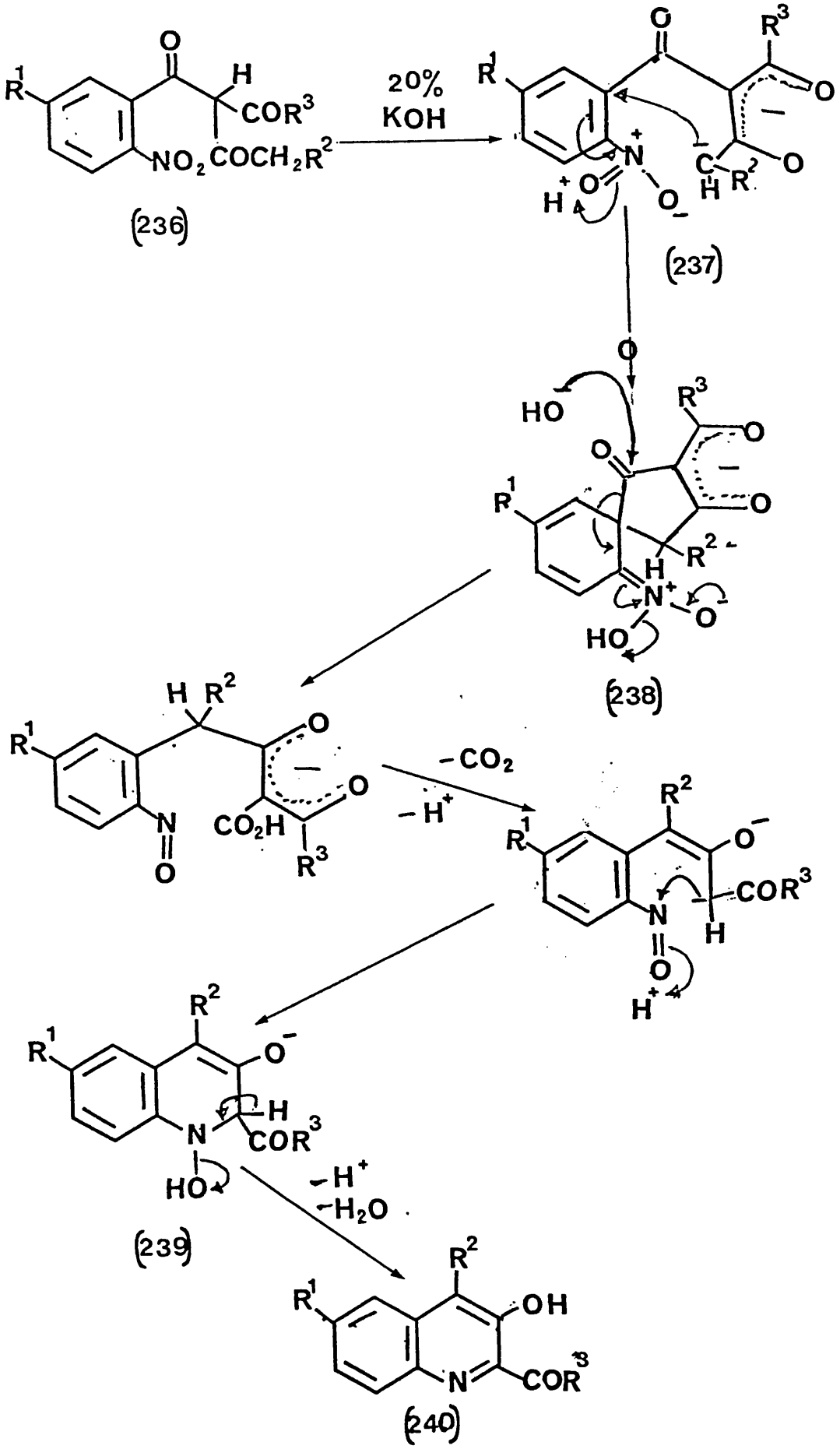
Synthesis of 2-Acyl-3-hydroxyquinolines

The formation of a spiro-intermediate in a base-catalysed cyclisation have been reported by Tennant and co-workers.[154]

Therefore when 3-(2'-nitrobenzoyl)pentane-2,4-dione (236, R^1=R^2=H,R^3=Me) was heated under reflux (0.5 h) with 20% w/v aqueous potassium hydroxide, the 2-acetyl-3-hydroxyquinoline (239a, Scheme 99) was obtained as the major product.

Cyclisations are readily explained in terms of a mechanism (Scheme 99) which involve the Smiles rearrangement. Thus, intramolecular nucleophilic attack at C-1' in the dicarbanion (237) affords the spiro-intermediate (238) and subsequently gave the 2-acetyl-3-hydroxyquinoline (240).

Many more examples of the spiro-cyclic-intermediates may be found in the literature and cover a wide range of reactions involving nitrene-induced aromatic rearrangements[155,156], reduction of nitro and nitroso-comounds[157-161], rearrangement of methoxylated phenylanthranils,[162] pyrolysis of 2-azidobenzoates[163], rearrangement of thebaine and codeine analogues[164-166], and the spirodiene rearrangements[167].



Scheme 99

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